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ROBOT-ASSISTED LYMPHADENECTOMY AND SENTINEL NODE BIOPSY IN HIGH RISK ENDOMETRIAL CANCER

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Robot-assisted laparoscopy and sentinel node biopsy in high risk endometrial cancer

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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To the women who briefly were my patients and taught me.

ABSTRACT

Surgery is standard treatment for early stage endometrial cancer (EC), the most common gynaecological malignancy in developed countries. Traditionally, surgery has been performed by laparotomy (LT). Comprehensive surgical staging, including pelvic (PLND) and paraaortic (PALND) lymph node dissection, is associated with morbidity and possible reduction in quality of life. Minimally invasive surgery (MIS) is associated with less morbidity, albeit newer MIS techniques, i.e. robot-assisted laparoscopic surgery (RALS), has not been compared with LT in a randomised setting. The sentinel lymph node technique is well established in other malignancies, however, the experience in EC is limited. The aim of this thesis was to evaluate if RALS for PLND and infrarenal PALND (IRPALND) in women with high risk EC is non-inferior to LT in harvesting lymph nodes, to investigate short- and long-term morbidity as well as quality of life. We also wanted to evaluate the sentinel lymph node biopsy concept as a diagnostic tool for detecting lymph node metastases (LNM).

In the RASHEC trial, we randomised 120 women with stage I-II EC with high-risk tumour features to hysterectomy, bilateral salpingo-oophorectomy, PLND and IRPALND by either RALS or LT between 2013 and 2016. Primary endpoint was paraaortic lymph node count. Patient-reported outcome (EORTC QLQ-C30 and the endometrial cancer module EN-24, EQ-5D for generic health status) was assessed before surgery and 12 months after surgery. Computed tomography (CT) was performed at baseline, 3 and 12 months after surgery. Patient characteristics were evenly distributed between the two groups. In the per protocol analysis of 96 patients, difference of means with a 95% confidence interval was within the non-inferiority margin for infrarenal paraaortic lymph node count (-1.6, 95% CI -5.78 - 2.57). No difference in perioperative complications (Clavien-Dindo classification) or readmissions to hospital within 30 days after surgery was found. RALS was associated with longer operation time ($p<0.001$) but less total blood loss ($p<0.001$), shorter hospital stay ($p<0.001$) and lower health care cost ($p<0.05$) compared to LT. We found no difference in self-reported lower limb lymphoedema, occurrence of lymphocysts, serious adverse events or admission to hospital for any reason between the two groups 12 months after surgery. Moreover, there was no difference in health-related quality of life.

The Sentinel node in High Risk Endometrial Cancer (SHREC- study) is a prospective non-randomised trial recruiting consecutive patients from two tertiary referral centres in Sweden (Lund and Stockholm) between 2014 and 2018 where each woman served as her own control. In total 261 patients underwent pelvic sentinel node biopsy followed by completion lymphadenectomy of which 257 were analysed. The sentinel lymph node biopsy algorithm applied in the SHREC-trial demonstrated a sensitivity for detection of LNM of 100% (95% CI 92-100) and a negative predictive value of 100% (95% CI 98-100).

This thesis demonstrates that RALS is non-inferior to LT in harvesting infrarenal paraaortic lymph nodes. RALS was associated with shorter hospital stay and lower health care cost and there were no evident differences in morbidity or quality of life. Consequently, we find RALS to be a valid option for comprehensive surgical staging including IRPALND in high risk endometrial cancer. The choice of surgical modality should be made based on surgeons' and patient preference.

The sentinel lymph node biopsy algorithm has a satisfactory bilateral mapping rate and complete detection of LNM, corroborating previous reports. Gold standard diagnostic lymphadenectomy in women EC should therefore be replaced by the less invasive sentinel lymph node biopsy.

LIST OF SCIENTIFIC PAPERS

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals as distinct from Arabic numerals:

I. Salehi S, Åvall-Lundqvist E, Legerstam B, Carlson JW, Falconer H

Robot-assisted laparoscopy versus laparotomy for infrarenal paraaortic lymphadenectomy in women with high-risk endometrial cancer: A randomised controlled trial

Eur J Cancer. 2017 Jul; 79:81–89.

II. Salehi S, Åvall-Lundqvist E, Brandberg Y, Johansson H, Suzuki C, Falconer H

Lymphedema, serious adverse events and imaging one year after comprehensive staging for endometrial cancer: results from the RASHEC trial.

Int J Gynecol Cancer. Accepted September 14th 2018

III. Salehi S, Brandberg Y, Åvall-Lundqvist E, Suzuki C, Johansson H, Legerstam B, Falconer H

Long-term Quality of life after comprehensive surgical staging of high-risk endometrial cancer- results from the RASHEC trial

Acta Oncol. 2018 Oct; 5:1-6

IV. Persson J, Salehi S, Bollino M, Lönnerfors C, Falconer H, Geppert B

Prospective assessment of sentinel lymph node biopsy in high-risk endometrial cancer (SHREC trial); a paradigm shift in surgical staging

In manuscript

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LIST OF ABBREVIATIONS

EC	Endometrial cancer
FIGO	International federation of gynaecology and obstetrics
ChT	Chemotherapy
RT	Radiotherapy
CR	Chemotherapy and radiotherapy (chemoradiation)
CCCR	Concomitant chemoradiation
GOG	Gynecologic Oncology Group (America)
MI	Myometrial Invasion
DNA	Deoxyribo Nucleic Acid
ESMO	European society of medical oncology
ESGO	European society of gynecologic oncology
ESTRO	European society of therapeutic radiotherapy and oncology
PLND	Pelvic lymph node dissection/lymphadenectomy
PALND	Paraaortic lymph node dissection/lymphadenectomy
RCT	Randomised controlled trial
MRC-ASTEC	Medical research council (United Kingdom) – a study in the treatment of endometrial cancer
EBRT	External beam radio therapy
SEPAL	Survival effect of paraaortic lymphadenectomy in endometrial cancer
LAP2	Laparoscopic approach to carcinoma of the endometrium
IRPALND	Infrarenal paraaortic lymph node dissection/lymphadenectomy
HRQoL	Health related quality of life
LLL	Lower limb lymphoedema
MIS	Minimally invasive surgery
LND	Lymph node dissection
LT	Laparotomy
FACT-G	Functional Assessment Cancer Therapy-General
SLN	Sentinel lymph node
SNBC	Sentinel lymph node biopsy concept
SNB	Sentinel lymph node biopsy
ICG	Indocyanine green
LNM	Lymph node metastases
NCCN	National comprehensive cancer network
ESMO	European society of medical oncology

LACE	Survival effect of paraaortic lymphadenectomy in endometrial cancer
RALS	Robot assisted laparoscopic surgery
SBU	Swedish agency for health technology assessment and assessment of social services
LAPPRO	Laparoscopic Prostatectomy Robot Open
PORTEC	Post-operative radio therapy in endometrial cancer
VBT	Vaginal brachy therapy
NCIC-CTG EN.5	National cancer institute of Canada - clinical trials group
OS	Overall Survival
JGOG	Japanese gynaecologic oncology Group
PFS	Progression free survival
ASTRO	American society for therapeutic radiology and oncology
RFS	Recurrence free survival
NSGO	Nordic society of gynaecologic oncology
EORTC	European organisation for research and treatment of cancer
MaNGO	Mario negri institute gynaecologic oncology group
RASHEC	Robot assisted surgery in high risk endometrial cancer
SHREC	Sentinel node in high risk endometrial cancer
SFOG	Swedish society of obstetrics and gynaecology
CT	Computed tomography
QoL	Quality of life
GCIG	Gynaecologic cancer intergroup
QLQ-EN24	Quality of life questionnaire-endometrial cancer 24
QLQ-C30	Quality of life questionnaire-core 30
CPP	Cost per patient
H&E	Hematoxylin and eosin
IHC	Immunohistochemistry
AJCC	American Joint Committee on Cancer
SD	Standard deviation
VAS	Visual analogue scale
UPP	Upper paracervical pathway
LPP	Lower paracervical pathway
MM	Micro metastases
ITC	Isolated tumour cells

1 INTRODUCTION

1.1 BACKGROUND

Endometrial cancer (EC) is the most common gynaecologic malignancy in the industrialised world with an estimated 100 000 diagnosed women annually in Europe [1]. In Sweden, EC is the sixth most common cancer and approximately 1400 new cases are diagnosed every year [2]. The incidence of EC is rising globally, though a decrease is evident in the Nordic countries [2,3]. Risk factors include an aging population, obesity, diabetes mellitus, null-parity, late menopause and unopposed oestrogen intake [4-8]. The median age at diagnosis in Sweden is 69 years. The most common histology is endometrioid EC, with a prevalence exceeding 80%. Uncommon histologic subtypes of EC include serous and clear cell adenocarcinomas, carcinosarcomas and other malignancies.

The overall relative 5-year survival rate in Sweden is 85% reflecting that most women have early stage of disease at diagnosis, Figure 1 [9]. However, prognosis even in presumed early stage of disease differs and depends on various factors including depth of tumour invasion into the myometrium, histological grading, tumour size, age, stage of disease and possible lymph node involvement [10-12].

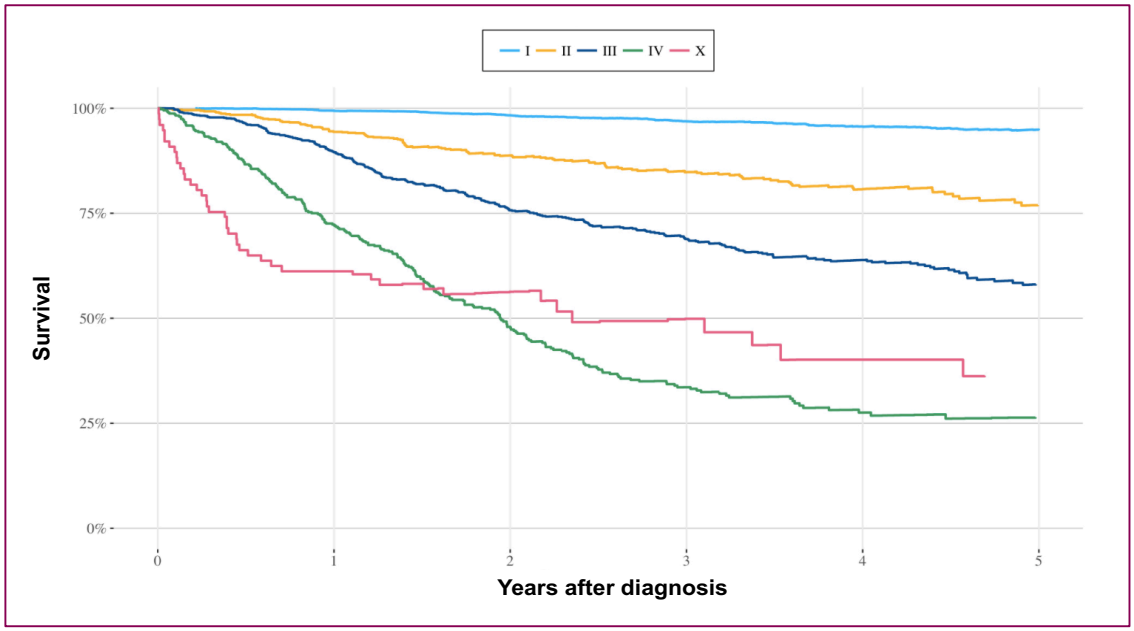

Figure 1. *5-year relative stage specific survival in women with EC diagnosed 2012-16 in Sweden. Stage X refers to patients without reported stage. Data publicly available from Swedish Quality Registry of Gynecologic Cancer, string Endometrial cancer [13].*

Staging of EC is surgical and according to the International Federation of Gynaecology and Obstetrics (FIGO), latest revised in 2009, see Figure 2 [14]. Grading is according to World Health Organisation classification of tumours into FIGO Grade 1 (43%), Grade 2 (37%) and Grade 3 (17%). [15].

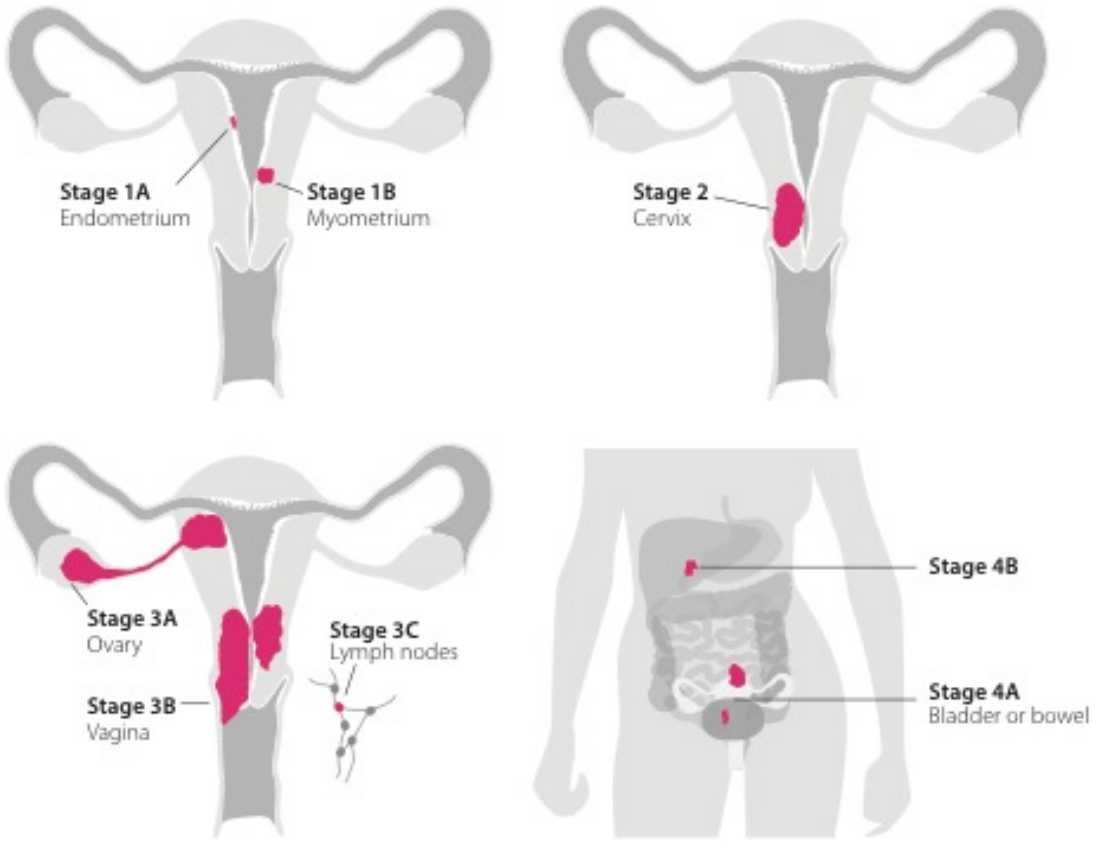

Figure 2. *Staging of endometrial cancer, FIGO 2009. For previous revisions see Appendix 9.1. Illustration by Mattias Karlén.*

There have been many attempts to predict which women with early stage disease that are considered "high-risk" (of recurrence, death of disease and dissemination of disease from inception) and whom might benefit from extended comprehensive surgical procedures (pelvic and paraaortic lymphadenectomy), adjuvant chemotherapy (ChT) and/or radiotherapy (RT).

Treatment of "low-risk" disease entails surgical extirpation of the inner genitalia (i.e. total hysterectomy and bilateral salpingo-oophorectomy) without adjuvant treatment as distinct from

"high-risk disease" where lymphadenectomy with different extents can be added and adjuvant treatment with ChT, RT, chemotherapy followed by RT (CR) or concomitant chemo-radiation (CCCR) is recommended.

There is an international consensus on the definition and treatment of so called "low risk" disease. However, opinions differ on the definition and treatment of "high risk" disease confined to the uterus. The underlying reasons are multi-factorial and will be discussed.

1.2 THE LYMPHATIC SYSTEM

The human lymphatic circulatory system accompanies the blood vessels. In contrast to the blood circulatory system there is no pump (heart) to help circulate its content. Instead, there is a low-pressure system with compression from muscles and valves within the lymphatic channels. The lymphatic system consists of nodes and lymphoid organs (spleen, thymus, tonsils, vermiform appendix and other lymphoid tissue in the gut).

Three main functions are attributed to the lymphatics. First, to drain plasma (blood without cells but with clotting factors) from the interstitium back to the blood stream (the blood capillaries loose about three litres of plasma daily to the interstitium). Second, it transports fat (chylomicrons) from the bowel to the blood stream. Third, it is part of the immune system containing lymph nodes and lymphocytes that cleans the plasma from microbes and tissue debris before re-entering the bloodstream. Cancer cells have the ability to enter the lymphatic system.

Surgical lymph node assessment is performed in all gynaecologic malignancies albeit to different extents and anatomic locations. Lymph node metastasis is the most common form of tumour dissemination in EC.

1.3 LYMPHADENECTOMY IN ENDOMETRIAL CANCER

1.3.1 History of lymphadenectomy as part of comprehensive staging

The first FIGO staging for EC was clinical and implemented in 1950. It consisted of two stages where stage I was cancer confined to the uterus and stage II cancer with growth outside the uterus [16]. In 1987, the American Gynecologic Oncology Group (GOG) published a descriptive surgical-pathologic staging study of 621 women with clinical stage I EC. 22% of patients had disease outside the uterus upon final histology and an association between tumour grade, depth of myometrial invasion (MI) and pelvic lymph node metastases was demonstrated (GOG 33) [17]. Three risk categories for pelvic lymphatic dissemination was suggested and defined as follows;

- Low risk (<5% risk of pelvic node metastases) intra-mucosal all grades, grade 1 with MI clear-cell and serous histology excluded
- Moderate risk (5-10% risk of pelvic node metastases) grade 2 with any MI, grade 3 < 50% MI
- High risk (>10% risk of pelvic node metastases) was grade 3 with > 66% MI + non-endometrioid histologies

Risk factors for paraaortic lymphatic dissemination was suggested and defined as follows:

- Low risk (<5% risk) all except high risk
- High risk Grade 3 tumours with >66% MI

As a result, lymphadenectomy was adopted into clinical practice although its efficacy (i.e. therapeutic effect of lymphadenectomy, effect of adjuvant RT and/or ChT) had not been proven in prospective trials. The revised FIGO staging became surgically based in 1988 [16]. The latest revision from 2009 also includes defined sub-stages for pelvic and/or paraaortic lymph node metastases [18].

There is no universal definition of "high risk". There are different opinions and risk stratification algorithms, most consist of different combinations of the histological subtype, grade of endometrioid histology, depth of MI, cervical stroma invasion, lympho-vascular space invasion, age of the patient, size of tumour and in Sweden also DNA-ploidy of the tumour cells. Moreover, different risk group categories before and after surgery exist. The ESMO-ESGO-ESTRO consensus guidelines from 2015 defines EC with endometrioid histology and myometrial invasion >50% or grade 3 endometrioid histology with <50% myometrial invasion as an intermediate risk group, women with grade 3 endometrioid histology with >50% myometrial invasion or Type 2 histology (clear cell, serous adenocarcinoma or carcinosarcoma) as high risk group [19].

The Swedish National Guidelines on EC, was published for the first time in 2012 and has since been revised. The definition of high-risk are as follows; non-endometrioid histology, grade 3 endometrioid histology, >50% MI, cervical stroma invasion or clinical cervical involvement [9].

1.3.2 Comprehensive surgical staging and definition of lymphadenectomy

According to the GOG surgical manual a comprehensive pelvic lymphadenectomy (PLND) is defined as removal of the nodal tissue from the distal half of the common iliac arteries, the anterior and medial aspect of the proximal half of the external iliac vessels and distal half of the obturator fat anterior to the obturator nerve. Paraaortic lymphadenectomy (PALND) is defined

as removal of nodal tissue over the distal inferior vena cava from the level of the inferior mesenteric artery to the mid right common iliac artery, removal of the nodal tissue between the aorta and left ureter from the mid inferior mesenteric artery to the mid left common iliac artery. There is no required number of harvested lymph nodes or proportion detected metastases in women subjected to lymphadenectomy. In 2008, the Mayo clinic published a study that challenged the definition of lymphadenectomy recommended by the GOG. It was demonstrated that more than 2/3 of paraaortic lymph node metastases were harboured above the inferior mesenteric artery, suggesting that the procedure had to be extended to the renal veins.

Furthermore, an adequate lymph node count of pelvic lymph nodes was suggested to be 35 and 17 for PALND. Moreover, they demonstrated that 16% of all patients with lymph node metastases had isolated paraaortic lymph node metastases [11]. In Europe, there is no detailed definition other than "systematic removal" of pelvic and para-aortic nodes up to the level of the renal veins and there are no required lymph nodes yield or proportion of detected lymph node metastases [19]. The Swedish National guidelines has the same definition [9].

In conclusion, the PLND and PALND in regards to comprehensive surgical staging in endometrial cancer is an ill-defined surgical procedure without consensus on exact anatomical boundaries and surgical quality.

1.3.3 Why is lymphadenectomy performed and does it offer a therapeutic benefit?

Two randomised controlled trials (RCT) have addressed the survival outcome of added pelvic lymphadenectomy vs no lymphadenectomy in EC without superior results. Benedetti-Panici et al. demonstrated that pelvic lymphadenectomy did not add any overall survival or disease-free survival benefit in early stage high risk EC (stage I with MI and endometrioid histology except grade 1 <50% MI assessed by per operative frozen section. 514 patients included), though lymphadenectomy provided a more accurate staging. With seemingly adequate surgery (lymph node count of 30, operation time 180 minutes), the study has been criticised for lacking strict criteria for adjuvant treatment [20].

The multicentre multinational (85 centres, four nations and 1408 patients included) MRC-ASTEC trial aimed to evaluate the potential therapeutic benefit of systematic pelvic lymphadenectomy. Women with presumed early stage EC regardless of risk profile were included and randomised to either extirpation of inner genitalia with or without resection of obturator and iliac lymphnodes. Furthermore, "sampling" of lymph nodes was allowed. There was no difference in survival between the groups. The study has been criticised for including low risk disease, the relatively short operation time (90 minutes), low pelvic lymph node count (median 12, 30% <10 lymph nodes) and low proportion lymph node metastases (9%). Moreover, 8% of the patients randomised to lymphadenectomy had no lymphadenectomy [21]. 5% of patients in the no lymphadenectomy group had lymph nodes removed with 27% of these positive for metastases. Moreover, women with postoperative high or intermediate risk based on

uterine factors alone (stage I A and B grade 3, non-endometrioid histology stage IC or IIA (FIGO 1988) regardless of positive lymph nodes (stage IIIC) or not were further randomised to receive external beam radiotherapy (EBRT) or not after surgery, which has been criticised since these patients at the time were thought to benefit the most of adjuvant radiation therapy [22].

The Japanese SEPAL study retrospectively compared women with EC confined to the uterus subjected to pelvic or pelvic and paraaortic lymphadenectomy [23]. The median age of 57 was relatively low but median pelvic and paraaortic lymph node count high (pelvic 34 vs 59 and paraaortic 0 vs 23).

There was a significant survival benefit shown in the group of women subjected to extensive comprehensive surgical staging although significantly fewer women had chemotherapy in the pelvic lymphadenectomy only group (27 vs 47%).

Chan et al. also conducted a retrospective review of more than 12000 women with endometrioid EC and found that women with high risk (and intermediate risk) EC subjected to lymphadenectomy had a better survival [24]. There is also retrospective data with opposite results[25]. A relatively recent updated Cochrane meta-analysis showed that lymphadenectomy in patients with presumed stage I EC did not confer superior survival outcomes [26].

1.3.4 Perioperative outcomes

One previous trial published 2009 has addressed postoperative complications and was also powered to detect potential differences between conventional laparoscopy and laparotomy after extirpation of the inner genitalia with pelvic and inframesenteric lymphadenctomy [27]. The LAP2 trial randomized 2616 women to either laparoscopy or laparotomy (2:1). 98 vs 99% had pelvic lymph node assessment with a median node count of 18 vs 17 and 94 vs 97% had inframesenteric paraaortic lymph node assessment with a median node count of 7 in both arms. The conversion rate from laparoscopy to laparotomy was 25%. There was no difference in intraoperative complications but the laparoscopy arm conferred shorter hospital length of stay and less use of antibiotics. In regards to postoperative complications measured by the United States, National Cancer Institute, Common Terminology Criteria for Adverse Events version 2.0 (NCI CTCAE 2.0) at six weeks postsurgery, laparoscopy was associated with fewer complications though no obvious differences were evident for specific complications except for postoperative ileus[28]. Nevertheless, this was the landmark study that changed the surgical standard of care in EC to minimally invasive surgery (MIS). A recent systematic review of surgical modalities in the treatment of EC showed fewer short term postoperative complications for robotic surgery compared to laparotomy [29].

The potential long-term complication rate and morbidity after PALND and infrarenal paraaortic lymphadenectomy (IRPALND) in EC is not known.

1.3.5 Lymphatic side effects

Lymphoedema is a chronic and progressive condition with negative impact on health-related quality of life (HRQoL) as well as health care costs [30,31]. Surgical resection of pelvic lymph nodes can result in lower limb lymphoedema (LLL). LLL can be objectified by measuring the lower limbs pre- and post-surgery, or subjectively assessed through different validated questionnaires. Self-perceived symptoms of lymphoedema, regardless of objectively measured symptoms or not, have been associated with decreased HRQoL and may be used to ascertain treatment effects [32]. Risk factors associated with LLL include lymphadenectomy, number of harvested pelvic lymph nodes, EBRT and obesity. Symptoms can arise year after treatment but are usually apparent after 3-5 months [33-38].

Since consensus on standardized measures and definition of LLL are lacking, dispersion of reported incidence and prevalence estimates after EC treatment is wide, ranging between 5-38% and 0-50% respectively [33-35,39,40].

After PLND and IRPALND, the proportion of patients with LLL, has been reported to be 18% and 37% for robot-assisted surgery and LT respectively [41,42].

Lymphocele is an organised collection of lymphatic fluid following lymphadenectomy. Lymphoceles may exert pressure on adjacent tissue or get infected. It has been suggested that MIS is associated with decreased incidence of lymphocele formation after PLND [43]. Zikan et al. prospectively followed 800 women with gynecologic malignancy that had undergone abdominal lymphadenectomy (59% PLND and 41% PLND and PALND) with follow up imagining every three months (pelvic and abdominal ultrasound) for two years [44]. 38% of patients in the cohort had EC and the majority of patients were subjected to laparotomy (80%). Moreover 92% were subjected to laparotomy. Proportion of patients with asymptomatic lymphocele was 20% of whom a third had symptomatic lymphocele formation.

There is no evidence supporting the use of abdominal drainage to avoid lymphatic complications after lymphadenectomy[45-47]. Since larger lymphatic channels closer to the cisterna chyli are transected during IRPALND, the risk of lymphatic ascites is theoretically higher compared to less extensive lymph node dissection (LND). For this reason, abdominal drainage might be of clinical value.

There is a lack of reports describing findings on abdominal computed tomography after IRPALND. Therefore, the clinician cannot be guided as to what could be expected. Moreover, no randomised trial has compared the frequency of lymphatic findings on computed tomography after IRPALND performed either by MIS or laparotomy (LT).

In conclusion, the lymphatic side effects related to the more extensive procedure of IRPALND in EC are largely unknown.

1.3.6 Health related quality of life and lymphadenectomy

The LAP2 study evaluated HRQoL after minimally invasive or open surgery with pelvic and inframesenteric paraaortic lymphadenectomy with the Functional Assessment Cancer Therapy-General (FACT-G) questionnaire [48,49]. At six-weeks post-surgery, there was a statistically significant difference in favour of laparoscopy ("physical functioning", "body image", "pain inference", "additional treatment related problems", "earlier resumption of normal activities") but no domain reached a clinically important difference. At six months' post-surgery, "body-image" alone remained significantly in favour of laparoscopy but still did not meet minimally important difference.

Zullo et al. randomised 84 women with stage I EC to either laparoscopy or laparotomy with HRQoL as main outcome using the Short Form Health Survey 36 (SF-36) questionnaire [50]. All women were subjected to PLND and 7% additional non-defined PALND. Laparoscopy conferred superior HRQoL outcomes at 1, 3 and 6 months after surgery.

The HRQoL outcomes associated with infrarenal paraaortic lymphadenectomy are unknown.

1.3.7 Sentinel lymph node biopsy

The sentinel lymph node (SLN) is the first lymph node adjacent to the lymphatic channels of the organ or tissue of interest. The sentinel node biopsy concept (SNBC) is well established in the surgical management of several malignancies including breast, melanoma and vulvar cancer, offering sufficient information on lymph node status for clinical decision making but with less morbidity [51-54].

In EC SLN mapping was first described in 1996, although the true potential of the technique has only been recognized during the last decade [55-57]. A major step forward in simplifying and standardising the SNBC in EC was the insight that a peri-tumoural injection could be abandoned in favour of cervical injection [58-61]. Traditionally, radiotracers (Technetium) with or without augmentation of dye have been used for sentinel node biopsy (SNB). Novel tracers such as fluorescent dyes (indocyanine green (ICG)) have been demonstrated to be superior [62-67]. In addition, ICG has the advantage of visualising the afferent lymphatic channels and possibly better identifying the most juxta-uterine and "true" sentinel lymph node, see Figure 3.

It has been suggested that the false negative rate of the SNB concept can be reduced from 15 to 2% if accompanied by an algorithm including resection of macroscopic suspicious lymph-node metastases irrespective of mapping or not and completion LND in case of mapping failure[68]. A Norwegian study with the aim to validate this algorithm used ICG and demonstrated a successful bilateral and unilateral mapping in 78 and 96% respectively[69].

Recent studies suggest that the diagnostic accuracy of SNB in EC may justify its use in clinical practice [63,70]. Rossi et al prospectively recruited 385 women with early stage EC without prior risk-categorisation with a majority being "low-risk" patients (75% MI<50%, 71% grade 1,2)[71]. Each woman served as her own control, with completion LND performed after SNB. The bilateral and unilateral mapping was 52 and 86% respectively. The sensitivity of the sentinel lymph node specimen was 97% and the negative predictive value close to 100%.

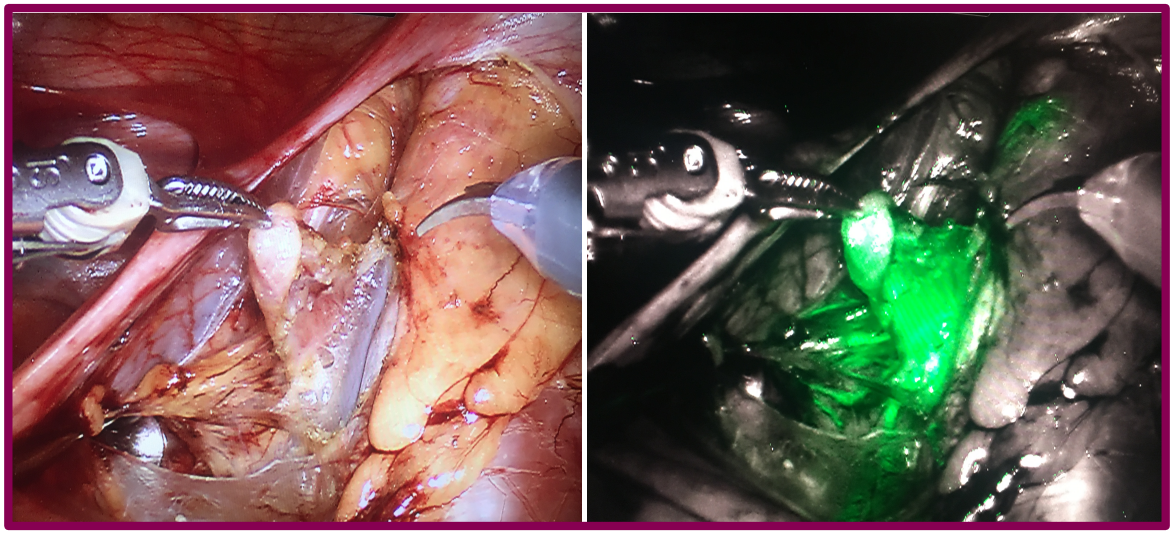

Figure 3. *Left; Forceps grasping the sentinel lymph node in the right hemi-pelvis. Right; Forceps grasping the sentinel lymph node in the right hemi-pelvis with near infrared display of ICG via Firefly mode®.*

Apart from detection rate, the rate of bilateral mapping of sentinel nodes and sensitivity (false negative rate included), constitute the most important aspects of the technique. One of the potential limitations of the SNB technique in EC is the potential failure to detect isolated paraaortic lymph node metastases (LNM) which constitute 15-20% of patients with lymphatic dissemination [11,17]. No study has yet properly evaluated the technique in this regard.

However, proportion isolated paraaortic LNM might be lower or potentially non-existent following pelvic sentinel node biopsy, since the pelvic lymph node assessment may become more precise [72,73].

Moreover, there is a risk of "empty packet syndrome", meaning that a macroscopically identified SLN do not contain lymphatic tissue upon microscopic evaluation, but the extent of this issue has not been explored.

Implementation of SNB would change the current surgical management dramatically by omitting preoperative risk prediction for lymph node metastases (including imaging to assess myometrial

infiltration), shorter operation time, lower health care costs and most importantly, potentially less perioperative morbidity and lymphatic side effects. There is a lack of scientific support for the SNB technique in women with early stage EC with high-risk features only.

SNB has been included as an option to full lymphadenectomy in the National Comprehensive Cancer Network (NCCN, an alliance of American cancer centres) guidelines [74].

The recommendation stated that sentinel node biopsy mapping may be considered "in select patients" but has now been expanded without reservation for patient selection. The European Society of Medical Oncology (ESMO) guidelines recommend SLN biopsy as an option in intermediate risk stage I EC (defined as grade 3 with <50% MI, or MI>50%)[75].

1.4 SURGICAL MODALITIES

1.4.1 Surgical modalities for pelvic and paraaortic lymphadenectomy

Laparoscopy was pioneered by Swedish internist Hans-Christian Jacobeus in the early 20th century by using a cystoscope [76]. The technique was adopted and developed by gynaecologists. In the early 1980's when the video screen was introduced, laparoscopy gained acceptance and became an established surgical treatment modality in the 90's with the first case-series reported on hysterectomy and lymphadenectomy; both pelvic and paraaortic [77-79]. Laparoscopic hysterectomy with lymphadenectomy for EC has since been evaluated in randomised trials against laparotomy. The GOG-LAP2 study showed that laparoscopic hysterectomy with PLND and PALND to the inferior mesenteric artery in women with EC conferred the same survival. The trial included women with early stage EC of all types, and no evidence in the "high-risk" early stage EC population has been provided.

The LACE trial confirmed the results of the GOG-LAP2 trial and has also shown less health care costs in favour of laparoscopy, though lymph node dissection (LND) was not mandatory and if performed, only PLND was required (PALND was optional) [80-82]. The proportion of patients subjected to lymphadenectomy was imbalanced (40 and 58% for laparoscopy and laparotomy respectively) and the extent of lymphadenectomy was not defined. Furthermore, the low proportion of patients with lymph node metastases (<3.5%) and low number of pelvic lymph nodes (10 and 11 for laparoscopy and laparotomy respectively), preclude conclusions regarding lymphadenectomy from this trial.

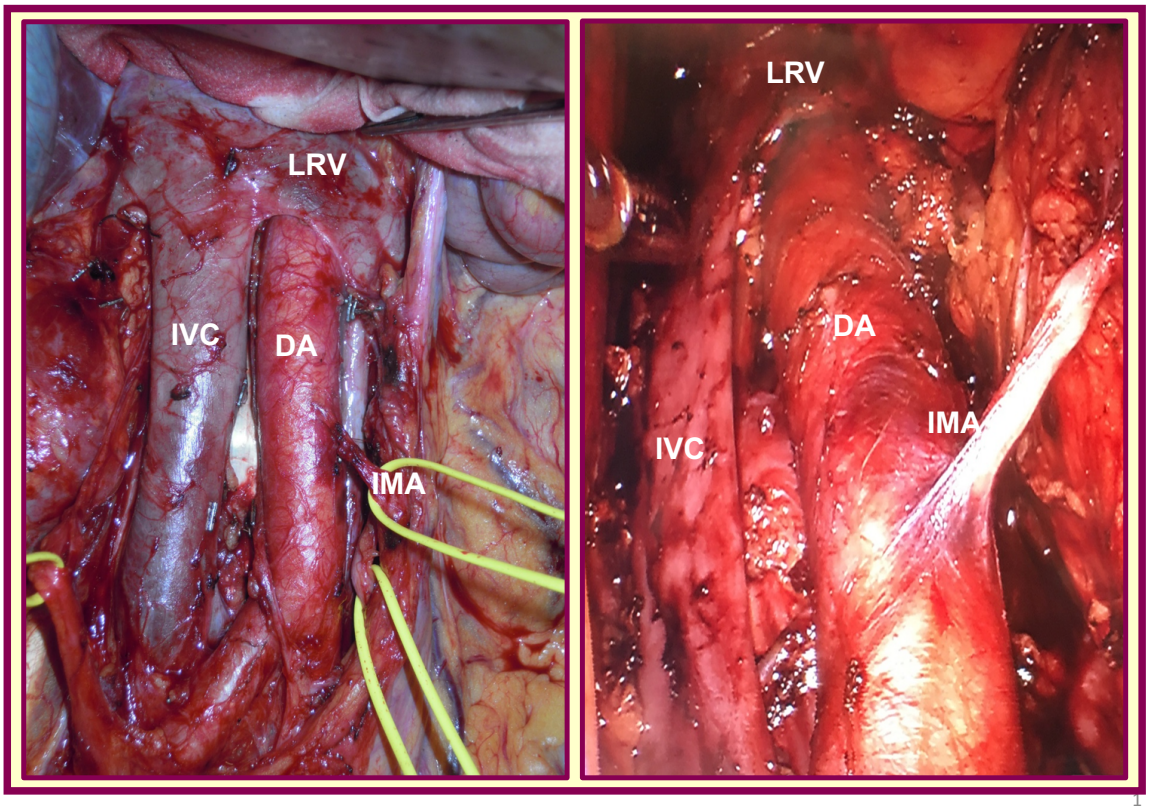

***Figure 4**. Left: the paraaortic field by laparotomy. Right: the paraaortic field by robot-assisted laparoscopic surgery. The cephalad border of an inframesenteric paraaortic lymphadenectomy is the IMA. The cephalad border of an infrarenal paraaortic lymphadenectomy is the LRV. Abbreviations: LRV, left renal vein; IVC, inferior vena cava; DA, descending aorta; IMA, inferior mesenteric artery.*

No randomised trial has compared the perioperative outcomes between MIS and laparotomy for the more extensive surgical procedure of infrarenal paraaortic lymphadenectomy. Infrarenal paraaortic lymphadenectomy as opposed to inframesenteric lymphadenectomy, involves an added surgical dissection of 5-7 cm cephalad, making the procedure extremely more demanding with the need of much greater area of dissection and surgical skill (see Fig. 4).

1.4.2 Robot- assisted laparoscopic surgery

The United States Food and Drug administration (U.S. FDA) approved Robot-assisted laparoscopic surgery (RALS) for gynecologic indications in 2005. The uptake of RALS has been dramatic with currently more than 4200 robotic systems worldwide[83].

This tremendous increase has been driven by several factors including the perceived superior surgical ergonomics (Fig. 5), the improved dexterity, and presumably a desire to embrace new technology. In addition, intense marketing by the only manufacturer has contributed to this development.

Even though RALS seems safe in terms of perioperative morbidity, there is a lack of scientific evidence to support the superiority over other surgical modalities from strictly medical aspects[84]. In addition, the investment cost for a robotic system is considerable and the effects on health care costs is a major concern.

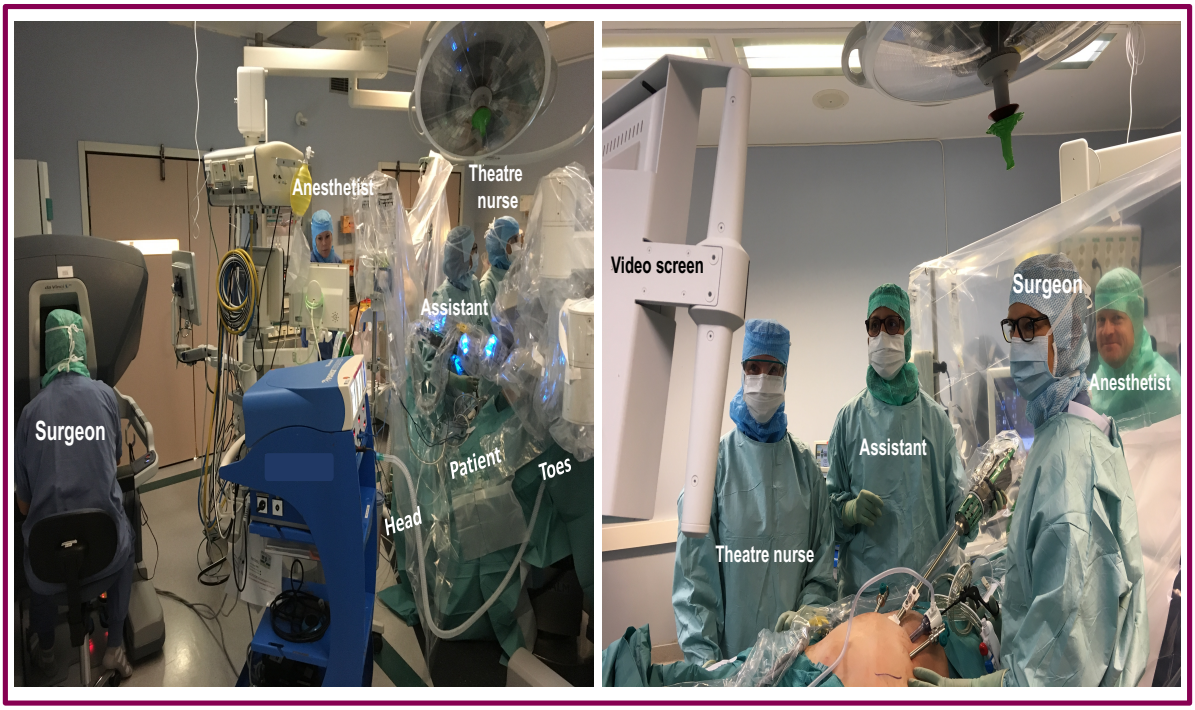

Figure 5. *Left: position of surgeon by robot-assisted surgery sitting in the consol. Right: position of surgeon by conventional laparoscopy, standing beside the patient.*

1.5 HEALTH CARE COSTS

It is stated as part of the Swedish health and Medical Care Act that "publicly financed healthcare should be organised to promote cost-effectiveness" (Chapter 4, § 1) [85]. There are different techniques of evaluating health care economics that are beyond the scope of this thesis, a summary is available at the Swedish agency for health technology assessment and assessment of social services (SBU)[86]. In contrary to pharmaceuticals, there is no investigative authority that scrutinises technical medical products in Sweden.

The Health technology assessment centre in Western Sweden Health Care Region evaluated RALS in five reports of which one specifically investigated benign gynaecological surgery and concluded that RALS could not be regarded as a cost efficient surgical modality [87].

A review of literature, analyzing 8 surgical procedures did not find any cost-effective benefits of RALS compared to other modalities except for radical prostatectomy[88]. Since, data from the LAPPRO (Laparoscopic Prostatectomy Robot Open) study, a prospective non-randomised controlled multi-center Swedish trial with primary objective to evaluate

urinary continence and erectile function between laparotomy (LT) and RALS conducted between 2008-2011, demonstrated that RALS increases cost per procedure by 3837 United States Dollars as compared to LT, (n=803, 1835 LT and RALS respectively) [89,90].

1.5.1 Robotic surgery in gynecologic oncology

Reynisson and Persson compared 51 women with cervical cancer subjected to radical hysterectomy and pelvic lymphadenectomy by LT with 180 subjected to RALS for. They concluded that RALS may confer equal costs after 90 procedures, given that 400 procedures are performed per robotic system annually. This translates to a high surgical proficiency and volume setting[91]. Their results were corroborated by Wallin et al[92]. Another Swedish study evaluating the healthcare cost of women with EC subjected to hysterectomy with pelvic lymphadenectomy by RALS vs LT (n=40, 48) using the same 7-year depreciation for the purchase of a robotic system as Reynisson and Persson and given 350 procedures annually, suggested equal costs between modalities[93].
The studies are small and observational why the results must be interpreted very cautiously. Furthermore, both studies are based on preconditions that can change, e.g. number of procedures, operation time, purchase price of robotic system. In conclusion, the cost efficiency of RALS has yet not been decisively demonstrated in a public health care system.

1.6 ADJUVANT TREATMENT

1.6.1 Adjuvant radiotherapy vs no adjuvant radiotherapy

Adjuvant radiotherapy in the context of both early and advanced stage EC has been explored in several randomised trials without superior survival benefits.

The GOG-99 (included surgical staging according to the GOG surgical manual) and PORTEC-1 trial (no lymphadenectomy performed) demonstrated that adjuvant pelvic EBRT in early stage EC reduced the rate of loco-regional recurrence but did not produce a survival benefit compared to no adjuvant treatment after surgery [94,95].

The PORTEC-2 trial (no lymphadenectomy) demonstrated that vaginal brachy therapy (VBT) was as effective as EBRT in reducing the loco-regional recurrence rate with less toxic side effects in women with early stage EC without compromising survival [96]. Further, the pooled analysis of the MRC-ASTEC (some had pelvic lymphadenectomy) and NCIC-CTG EN.5 (no lymphadenectomy) study which randomised women with stage I-II intermediate or high risk to either pelvic EBRT or no EBRT confirmed the results of the previous trials with no difference overall survival (OS) [97].

1.6.2 Adjuvant chemotherapy or concomitant chemo-radiation vs radiotherapy

1.6.2.1 Early stage disease

The Japanese Gynecologic Oncology Group (JGOG) randomised women with stage IC-IIIC according to FIGO 1988 staging to either ChT or pelvic EBRT. A subgroup analysis of women with high-intermediate risk (stage IC, >70 years, grade 3 endometrioid or stage II or IIIA with >50% myometrial invasion) had a significant better survival when allocated to ChT (90 vs 74% at 5 years). 96% of patients in this study had PLND and 29% PALND with 12% stage IIIC disease in the total group, which suggests an adequate surgical staging. However, patients with stage IIIC disease were not included in the subgroup of patients that benefited from ChT [98].

Maggi et al. allocated women with high risk disease (FIGO 1988 stage IC grade 3, stage II grade 3 with >50% MI and stage III, pelvic and "lumbo-aortic" lymphadenectomy was optional) to either pelvic EBRT or ChT, there was no difference in OS or progression free survival (PFS) [99].

The more recent GOG 249 study presented at the American Society for Therapeutic Radiology and Oncology (ASTRO) randomised women with high or high-intermediate risk stage I-II EC to either ChT and VBT or pelvic EBRT, pelvic and paraaortic surgical staging was optional. There was no difference in recurrence free survival (RFS) at 5 years and 3-year OS. The proportion of patients with stage IIIC disease and subgroup analysis are awaited [100].

1.6.2.2 Advanced stage disease

The GOG-122 study randomised women with stage III and IV (without extra-abdominal metastases) EC to either whole abdominal radiotherapy or chemotherapy, patients with residual disease <2cm after surgery were included and all patients were surgically staged with lymphadenectomy according to the GOG surgical manual [101]. 65% of women with stage III had stage IIIC and overall, 49% of included women had stage IIIC disease. The results were in favour of ChT for both OS and PFS, though subgroup analysis for stage IIIC exclusively was not significant.

Högberg et al. pooled analysis of two RCTs (NSGO/EORTC trial and MaNGO-Iliade trial) showed a superior PFS (78 vs 69%) in favour of ChT and EBRT vs EBRT alone for women with ill-defined stage I high risk, stage II, IIB stage IIIA-IIIC EC. In subgroup analysis, endometrioid histology remained significant but not non-endometrioid. There was no difference (but close to significant) in OS (82 vs 75%). Furthermore, there was a significant difference in cancer specific survival in favour of ChT + EBRT. Surgical staging was optional (para aortic lymph node metastases was an exclusion criteria) and 26% of included patients had pelvic lymphadenectomy [102]. Moreover, there was no benefit in favour of ChT+EBRT in women subjected to LND.

The PORTEC-3 trial demonstrated that CCCR followed by ChT vs pelvic EBRT only, reduces the 5-year RFS (76 vs 69%) but there was no difference in OS. The 5-year OS for patients with stage III disease only was better for the ChT+EBRT group (79 vs 70%) though not significantly. Unfortunately, the proportion of patients with stage IIIC disease exclusively was not reported and only 15% of patients had non-defined lymph node assessment since lymphadenectomy was optional [103].

Results from the GOG 258 trial was presented as abstract in 2017 [104]. Women with stage III/IVA, stage I-II with serous or clear cell histology with positive peritoneal washings were randomised to either CCCR followed by ChT or ChT only. Again, surgical staging with lymphadenectomy was optional and residual disease of <2cm was allowed. The final results showed no difference in RFS between the groups, but less distant recurrences in women allocated to ChT only (21 vs 28%, not significant) as opposed to less loco-regional recurrences in women allocated to CCCR (vaginal recurrence 3 vs 7%, pelvic and paraaortic recurrence 10 vs 21%). Proportion patients with stage IIIC, OS and possible subgroup analyses are awaited.

1.7 SUMMARY

2017 marked the 30th anniversary of the GOG-33 study that created the foundation for the practice of lymphadenectomy in endometrial cancer. Since, the role of this surgical procedure and its extent is still debated and practice differs globally [105].

Despite several large RCTs, standard of care in women with high risk EC is still subject to debate. The main reasons behind the controversies include non-standardised surgery or adjuvant treatment, diverse definitions of risk and indications for added lymphadenectomy. Though proven non-efficient in multiple large RCTs, the use of adjuvant EBRT continues to be recommended in early stage disease. In patients with stage III/IV EC, evidence in favour of chemotherapy or concomitant chemo-radiation is growing, although the efficacy in stage IIIC disease only remains to be proven.

The indication for lymph node dissection in EC confined to the uterus is still for staging and to "tailor" adjuvant treatment, however, evidence of the efficacy of any adjuvant treatment in stage IIIC solely is yet to be provided. Indeed, it has been demonstrated that risk factors other than lymph node metastases (age, grade, depth of MI) are independently more important in terms of survival[106,107]. Moreover, risk of recurrence might be high based on uterine factors alone in spite of negative lymph node assessment[94]. The practice of lymphadenectomy can thus be disputed. Similarly, pelvic an infrarenal paraaortic lymphadenectomy continues to be an ill-defined and strictly diagnostic surgical procedure.

Based on RCTs, minimally invasive surgery seems safe and has replaced laparotomy as the preferable route of surgical access because of less perioperative complications. Whether minimally invasive surgery/RALS is safe in IRPALND is not known. Furthermore, the side effects and HRQoL related IRPALND is also largely unknown.

The sentinel lymph node biopsy concept has emerged as a promising alternative to full pelvic lymphadenectomy, whether it is a valid diagnostic tool for lymph node assessment in women with high-risk early stage endometrial cancer is yet to be established.

A summary of important and/or influential studies and clinical trials is provided in Appendix 9.2.

2 OVERALL AIMS OF THE THESIS

The overall aim of this thesis was to evaluate different surgical techniques for lymph node assessment, as part of comprehensive staging, in women with high-risk early stage endometrial cancer to reduce morbidity without compromising diagnostic accuracy.

Specific aims of this thesis were:

1. To investigate if robot-assisted laparoscopic surgery (RALS) was non-inferior to laparotomy (LT) in harvesting infrarenal paraaortic lymph nodes (primary outcome). To compare number of pelvic node count, perioperative outcomes and health care cost as secondary outcomes.

2. To examine serious adverse events, observations on imaging and evaluate self-reported lower limb lymphoedema at 12 months after surgery (RALS or LT) and explore the impact of abdominal drain.

3. To evaluate long-term health-related quality of life related to the extirpation of inner genitalia with pelvic and infrarenal paraaortic lymphadenectomy by RALS or LT.

4. To explore if the sentinel node biopsy concept with injection of indocyanine green in the uterine cervix is a valid diagnostic method in comparison to a full pelvic lymphadenectomy in women with with high-risk early stage endometrial cancer.

3 PARTICIPANTS AND METHODS

3.1 PARTICIPANTS

3.1.1 Paper I-III

The **R**obot-**A**ssisted **S**urgery in **H**igh-risk **E**ndometrial **C**ancer (RASHEC) study is a randomised, open, parallel, single-institution non-inferiority trial performed at the Department of Obstetrics and Gynaecology, Karolinska University Hospital, the only tertiary referral centre in Stockholm, Sweden. The hypothesis was that RALS is non-inferior in paraaortic lymph node yield but with the advantage of offering less perioperative morbidity, shorter hospital stay, less lymphatic side effects and better HRQoL.

Between May 2013 and July 2016, 143 consecutive women were assessed for eligibility. Inclusion criteria were: age between 18-75 years, histological confirmed endometrial cancer, presumed FIGO stage I or II, preoperative high-risk tumour, performance status 0-1 according to Eastern Cooperative Oncology Group (ECOG). Exclusion criteria were: preoperative imaging indicating extra-uterine spread, medically unfit for surgery, ongoing anti-tumoural treatment (except hormonal therapy e.g. aromatase inhibitors and selective oestrogen receptor modulators, SERM, e.g. Tamoxifen), inability to comply to the protocol, unable to understand Swedish. Disseminated disease diagnosed during surgery was also an exclusion criteria. In total, 120 patients were included in the study.

3.1.2 Paper IV

The **S**entine**L** **N**ode in **H**igh **R**isk **E**ndometrial **C**ancer (SHREC) study is a prospective single-arm non-randomised controlled trial performed at two tertiary referral centres in Sweden (Skåne University Hospital and Karolinska University Hospital). Consecutive women with high risk endometrial cancer were recruited between June 2014 and May 2018. Each woman served as her own control. The inclusion criteria were: age 18-85 years, histological confirmed endometrial cancer, preoperative high-risk tumour, able to understand and sign an informed consent in Swedish language. Exclusion criteria were: performance status ≥3 according to ECOG, previous lower limb lymphoedema, evidence of disseminated and/or locally advanced disease, surgical contraindication to a laparoscopic approach or lymphadenectomy at the surgeon's discretion, contraindication to minimal invasive surgery at anaesthetist´s discretion, allergy to iodine, known liver disease, bleeding disorder or mandatory antithrombotic treatment. In total, 275 patients gave informed consent and were included in the study.

3.2 METHODS

3.2.1 Paper I-III

3.2.1.1 Study design

The RASHEC study is a randomised, open, parallel, single-institution, non-inferiority trial. Randomisation was made after written informed consent at the outpatient clinic, using a complete block design with 20 sealed envelopes at a time and the patient drawing a sealed envelope. Masking was not performed due to the nature of the treatment. Patients were randomly assigned (1:1 ratio) to undergo hysterectomy, bilateral salpingo-oophorectomy (SOEB), pelvic (PLND) and infrarenal paraaortic lymph node dissection (IRPALND) through laparotomy (LT) or robotic-assisted laparoscopic surgery (RALS).

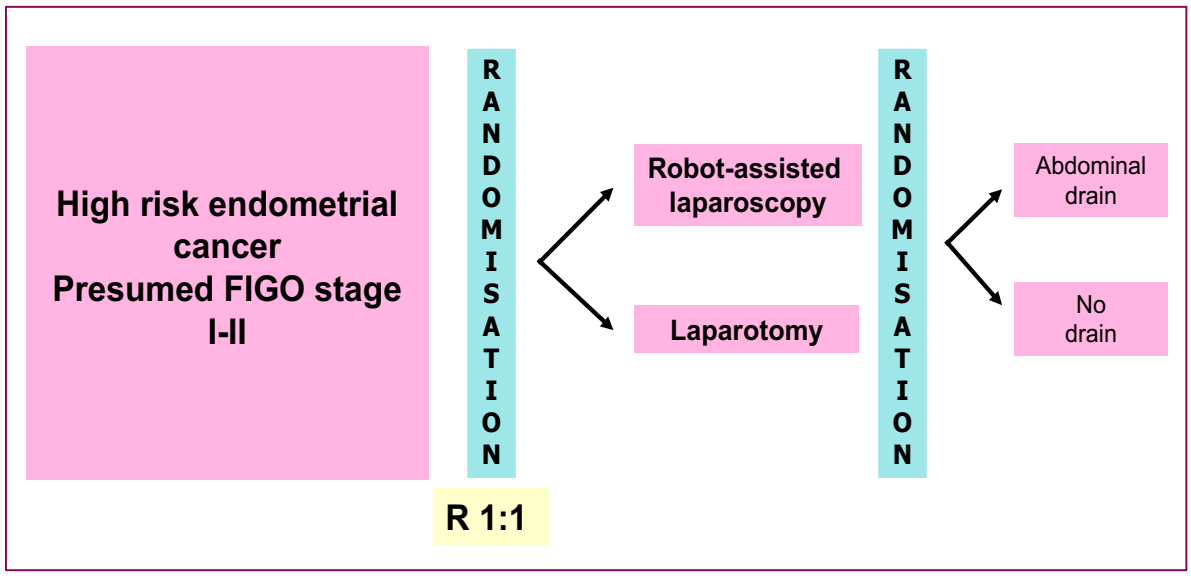

Figure 6. *Study schema for the RASHEC trial. Abbreviations: R, Ratio.*

A second randomisation was performed simultaneously to abdominal drain or no abdominal drain at time of surgery. The study schema and overall schedule of the RASHEC trial are presented in Fig. 6 and 7.

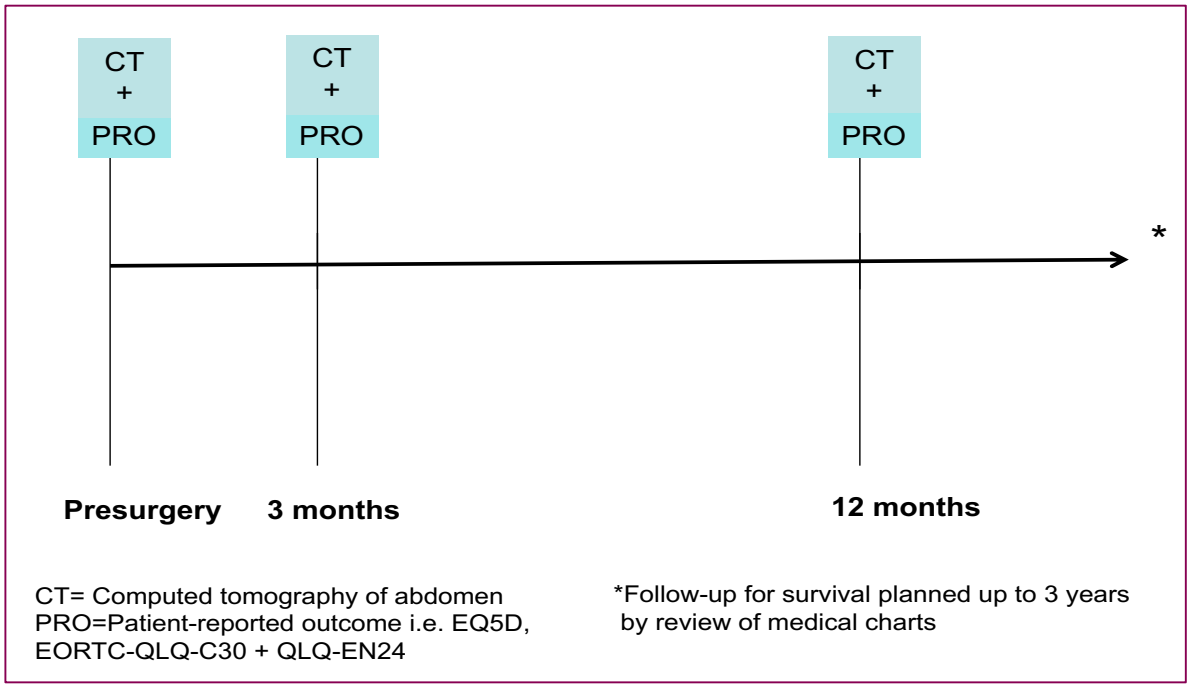

Figure 7. *Overall study schedule of the RASHEC trial*

3.2.1.2 Surgical procedures

In women randomised to LT, a full midline laparotomy was performed with access to the para-aortic lymph nodes gained through the Cattell-Braasch manoeuvre, mobilizing the right colon and duodenum/pancreas [108]. In women randomized to RALS, a double-side docking procedure was performed (daVinci Si system, Intuitive Surgical Inc., Sunnyvale, California, USA).

A passive abdominal drain was placed in women randomised to receive drain.

3.2.1.2.1 Definition of lymphadenectomy and participating surgeons

PLND was defined as the dissection and extirpation of all fatty tissue and nodes from half of the common iliac vessels cephalad, the external iliac vessels to the circumflex vein caudad and in the obturator fossa above the obturator nerve. Although the definition excludes the cephalad part of the common iliac vessels, all women underwent complete resection of the common iliac nodes. IRPALND was defined as dissection and extirpation of all fatty tissue and nodes up to the left renal vein cephalad, the common iliac bifurcation caudad, performed interaortocaval, paraaortal and paracaval. The lateral paraaortic border being the left gonadal vein and the paracaval lateral border the ureter. The depth of the dissection inter-aortocavally was the anterior spinous ligament and the iliopsoas muscle paraaortic and paracavally. Complete retro-caval and retro-

aortic dissection was optional. Five surgical gynecologic oncologists performed the laparotomies and one all RALS. All surgeons were certified subspecialists in Gynecologic Oncology by the Swedish Society of Obstetrics and Gynecology (SFOG).

3.2.1.3 Imaging

Computed tomography (CT) scans of the abdomen was performed routinely at baseline (pre-surgery) and at three and 12 months after surgery as per study-protocol. All CT scans were performed using commercially available multidetector CT after administration of intravenous contrast agent. The assessment protocol included: presence of suspicious lymph nodes, lymphocysts, ascites, recurrence and other potential abnormal findings. All CT-scans were re-reviewed by a specialized radiologist with more than 10 years' experience in diagnostic oncological imaging.

3.2.1.4 Long term serious adverse events and admissions to hospital for any reason

Medical charts were reviewed for admissions and long-term adverse events for any reason. Clavien-Dindo classification grade ≥ 3 was considered a serious adverse event, which corresponds to a minimum requirement of surgical, endoscopic or radiological intervention (grade 3) up to death of a patient (grade 5) [109]. The variables were assessed at day 31-365 post-surgery and per patient.

3.2.1.5 Self-reported lower limb lymphoedema

In accordance with the recommendations of quality of life (QoL) and patient reported outcomes from the Gynecologic Cancer Intergroup (GCIG), we used two questions from the QLQ-EN24 questionnaire to capture symptoms of lower limb lymphoedema (LLL) i.e. "*Have you had swelling in one or both legs*" and "*Have you felt heaviness in one or both legs*" with answers from "not at all", "a little", "quite a bit" and "very much" [110]. The association of previously reported and exploratory predictors of self-reported LLL were assessed. The agreement between lymphatic "side-effects" objectively measured by CT at 12 months and self-reported LLL was assessed.

3.2.1.6 Questionnaires

To assess patient-reported outcomes and health-related quality of life, three validated questionnaires (EORTC QLQ-C30, QLQ-EN24 and EQ-5D-3L) were used and distributed to the patients before surgery (baseline), at three and 12 months after surgery. The questionnaires were either given to the patient at the clinic or sent home by conventional mail together with prepaid return envelopes.

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) includes overall quality of life (global health status), five functional scales (physical; role; emotional; cognitive; and social), three symptom scales (fatigue; nausea/vomiting; and pain), and six single items (dyspnoea; insomnia; appetite loss; constipation; diarrhoea and financial difficulties). The EORTC QLQ-C30 is considered to have good psychometric qualities and has been validated in Swedish [111,112].

The EORTC endometrial cancer supplementary module (QLQ-EN24) [111,113] includes three functional scales (sexual interest; sexual activity; sexual enjoyment), five symptom scales (lymphoedema; urological; gastrointestinal; poor body image; vaginal) and five single items (pain in back and pelvis; tingling/numbness; muscular pain; hair loss; taste change).

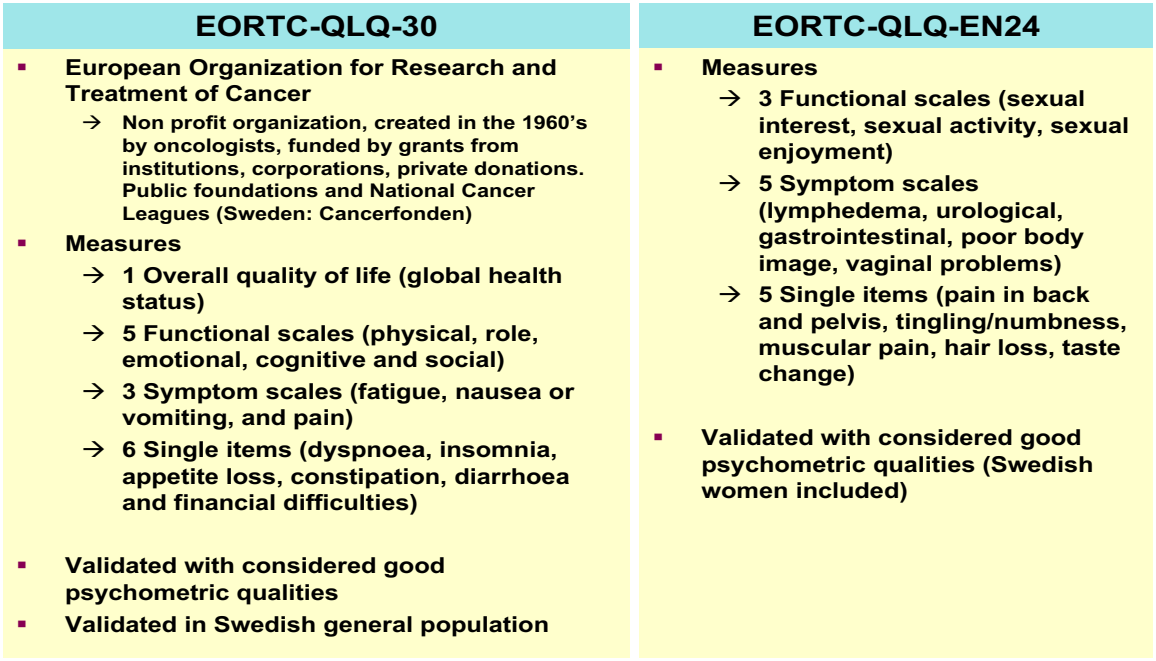

Figure 8. *Overview of the main questionnaires in the RASHEC trial*

The QLQ-EN24 has also been validated in two international studies showing good psychometric qualities, the Swedish version of the questionnaire was part of the first validation study [113,114]. The response format for both questionnaires is on a four-point scale, from 1 (Not at all) to 4 (Very much), except for two items in EORTC QLQ-C30 which are scored on a seven-point scale. A high score on the functional scales and global quality of life represents a high level of functioning and quality of life. A high score on the symptom scales/items represents a high level of symptoms. An overview of the EORTC questionnaires are presented in Fig. 8.

The EQ-5D-3L questionnaire, introduced in 1990 from the EuroQoL group, measures non-disease specific health status [115]. It encompasses five questions regarding "anxiety and depression", "pain/discomfort", "usual activity", "self-care" and "mobility" with three levels of answers; "no problems", "some problems" and "extreme problems". In the additional visual analogue scale (VAS), patients are asked to report their global health state in a scale from 0-100. The Swedish version of the questionnaire has been validated [116].

3.2.1.7 Cost per patient

Healthcare costs related to LT or RALS were calculated using the regional case-costing system (cost per patient, CPP). The total cost included all associated costs of ward care (e.g. staff, radiology, laboratory, medication) as well as costs related to activities performed in the operation theatre (all surgical instruments and draping included), postoperative care and pharmaceuticals. To calculate the additional cost specific for robot-assisted surgery, a 7-year depreciation for the robotic system and an annual caseload of 350 procedures/system were assumed.

We converted Swedish Crowns (SEK) to United States dollars (USD) using the 2013 currency rate (US $1 = 6.51 SEK) and SEK to Euro (€) using the 2013 currency rate (€ 1= 8.33 SEK). Costs related to complications within 30 days after surgery were included in the analyses.

3.2.2 Paper IV

3.2.2.1 Study design

The SHREC study is a prospective single-arm non-randomised controlled trial.

3.2.2.2 Primary outcome

Primary outcome measure was the diagnostic accuracy of our proposed sentinel lymph node biopsy algorithm as compared to gold standard LND for the detection of pelvic lymph node metastases. The diagnostic accuracy was defined by the sensitivity and negative predictive. Moreover, the sensitivity of the sentinel lymph node specimen and the NPV of successfully mapped women only.

3.2.2.3 The sentinel lymph node procedure

Enrolled women were scheduled for hysterectomy, bilateral salpingoophorectomy, pelvic sentinel lymph node biopsy and full pelvic and infrarenal paraaortic lymphadenectomy. A full pelvic lymphadenectomy only was permitted if indicated, e.g. advanced age or severe comorbidity. The surgeries were performed by robot-assisted laparoscopic surgery (RALS) using a da Vinci® Si or Xi Surgical System (Intuitive Surgical, Sunnyvale, CA, USA).

Before entering the abdomen, indocyanine green (2.5mg/mL) was injected in the submucosa and stroma of the cervix uteri at 2-4-8 and 10 o'clock. At each injection site, 0.25mL (0.625 mg ICG) was administered, with a total dose of 2.5 mg (Fig. 9). After the injection, a fornix presenter was placed (without any intracervical device) as per usual.

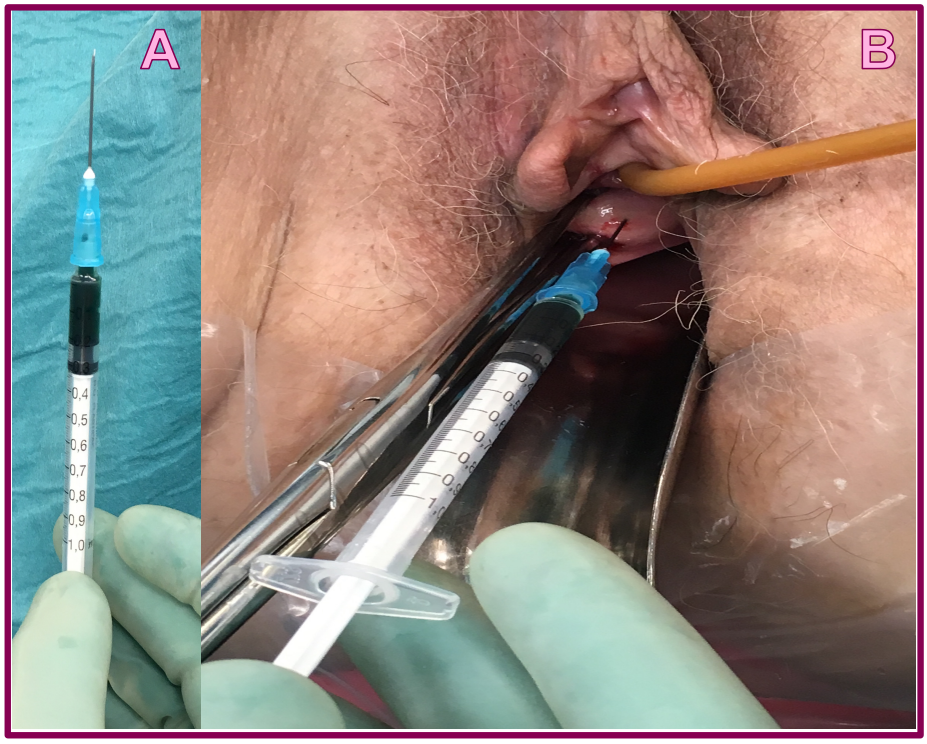

Figure 9. *Injection of ICG in the uterine cervix. A. Syringe with diluted ICG. B. Uterine cervix grasped with Schröder forceps, yellow tube is the urinary catheter, injection of ICG in uterine cervix at 2 o'clock.*

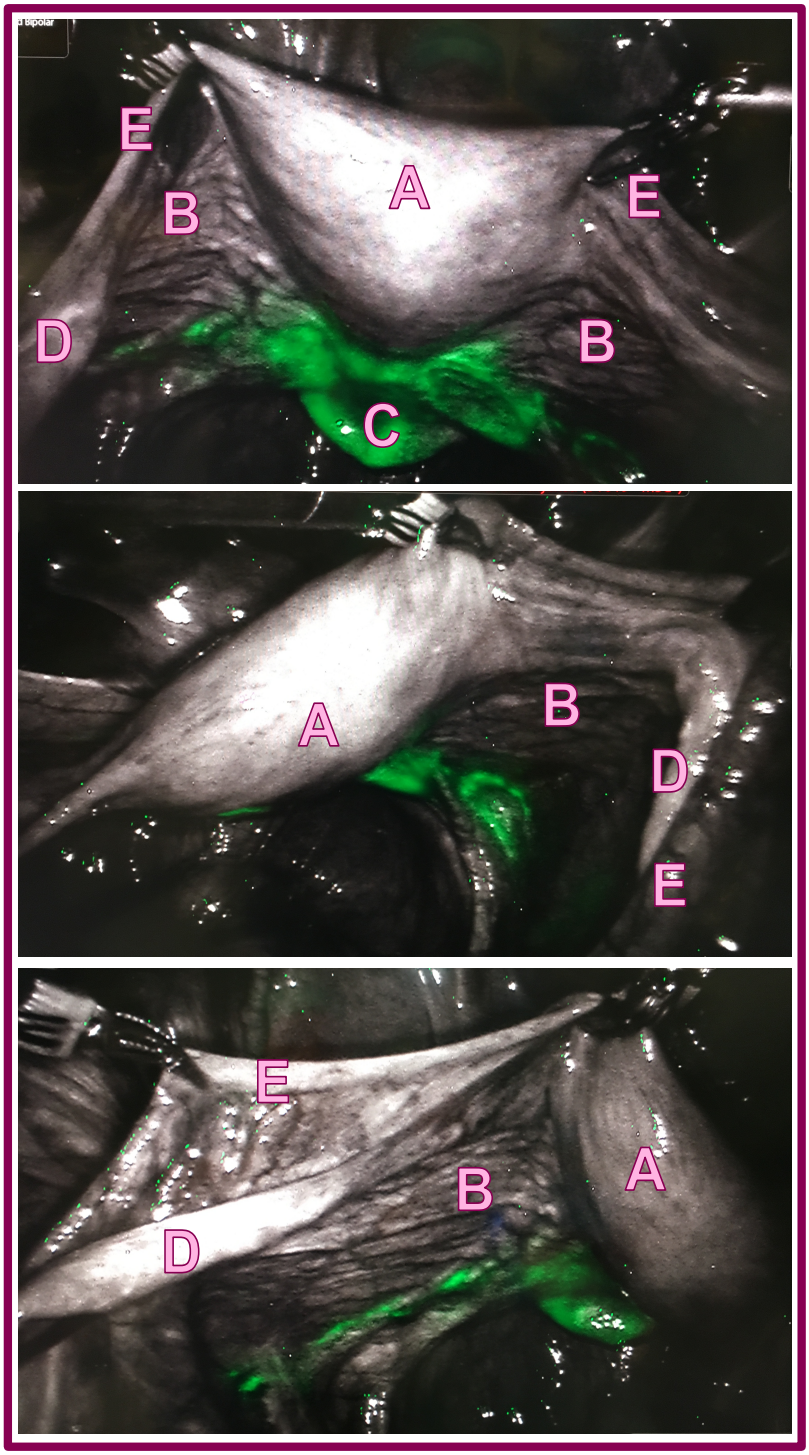

Figure 10. *Transperitoneal display of florescent ICG in the upper para-cervical pathways with fire-fly camera mode. Top, overview. Middle, right side. Bottom, left side. A; Posterior uterine fundus. B; Broad ligament. C; Uterine Cervix. D; Ovary. E; Fallopian tube.*

After entering the abdomen, fluorescence imaging with FireFly® Mode was used to identify the upper paracervical lymphatic pathway (UPP) along the uterine artery to the external and obturator nodes, continuing lateral to the common iliac artery to the inframesenteric paraaortic nodes. The lower paracervical pathway (LPP) medial to the internal iliac artery to the internal iliac and presacral nodes and continuing medial to the common iliac artery to the inframesenteric paraaortic area.

The display of ICG (Fig. 10) in the respective pathways was evaluated a minimum of 10 minutes after the injection of ICG, first trans-peritoneal and if not seen, after opening of the retroperitoneal pelvic avascular planes starting with the pre-sacral, para-vesical and para-rectal planes leaving the lymphatics intact with the aid of switching between white light and FireFly Mode. A second ipsilateral injection (0,25mL ICG) at 3 and 9 o'clock was made if no sentinel pathway could be visualised.

The pelvic sentinel lymph nodes (SLN) were defined as the juxta-uterine ICG positive node with an afferent ICG positive lymphatic channel in each of the UPP and LPP respectively on each pelvic side with the possibility of parallel lymphatics in the UPP to the external and obturator areas (Fig. 11). These SLN were defined as **SLN type 1.**

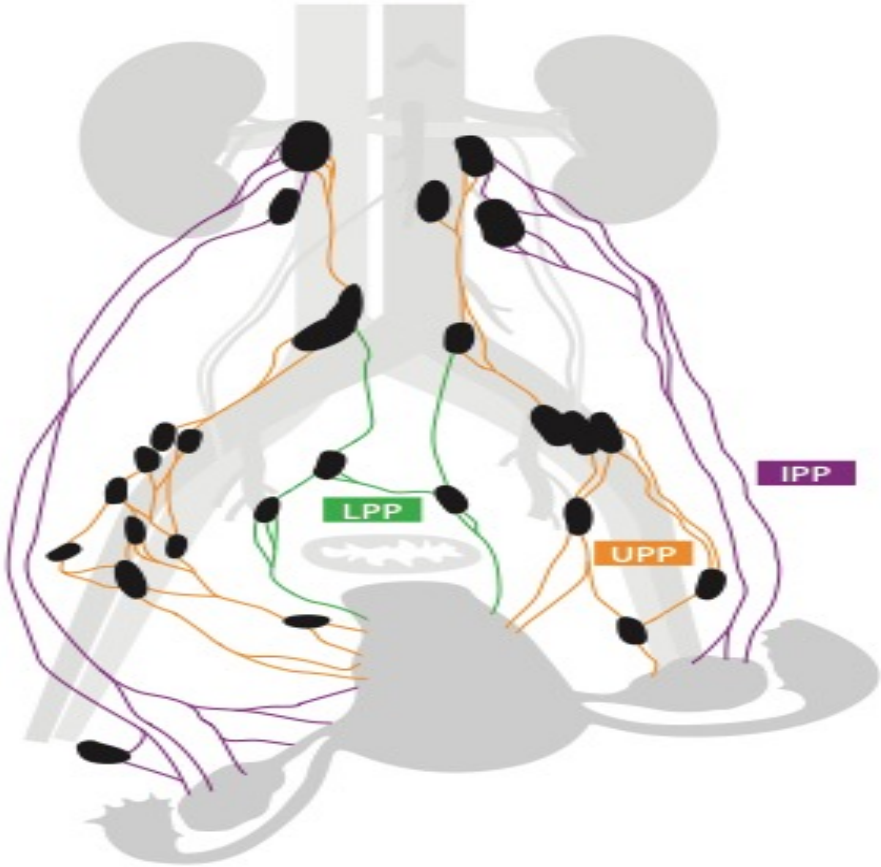

Figure 11. *The afferent lymphatic pathways draining the uterine corpus. Abbreviations: LPP, lower paracervical pathway; UPP, upper paracervical pathway; IPP, infundibulo-pelvic pathway. Illustration by Mattias Karlén.*

In case of a ICG positive lymph vessel where no nodes were ICG positive in that pathway, the node where the ICG positive lymphatic channel ends was defined as **SLN type 2**. Nodes macroscopically suspect of metastatic disease was defined as **SLN Macro** regardless of ICG uptake. After surgical resection of the sentinel lymph nodes, a completion compartmental

lymphadenectomy was performed with a rigorous labelling protocol and sent to the pathology department.

3.2.2.4 Pelvic sentinel lymph node algorithm

The algorithm comprised assessment of the UPP and LPP in both hemi-pelvises together with resection of all macroscopic suspicious lymph nodes regardless of mapping success or not. Reinjection of ICG tracer in the uterine cervix was allowed in case of uni- or bilateral non-display.

3.2.2.5 Histopathological assessment

Examination and evaluation of SLNs was performed by a restricted number of pathologists under the supervision of a gynecologic reference pathologist according to a standardized protocol. All macroscopically identified sentinel lymphoid tissue was embedded and bisected if the minimum thickness exceeded 3 mm. Ultrastaging using hematoxylin and eosin staining (H&E) was performed in five sections at three different levels, 200 μm apart, if the maximum diameter of the sentinel node tissue exceeded 1 mm. Immunohistochemistry (IHC) with staining for pan-cytokeratin and cytokeratin MNF 116 was performed.

Non-SLNs with a thickness less than 3 mm were embedded entirely and for nodes exceeding 3 mm at least half the node was embedded. Non-SLNs were stained for H&E but was not subjected to IHC.

The pathologists were not blinded to the results of SLNs and non SLNs when performing their assessment.

3.2.2.5.1 Definition of lymph node metastases

For the definition of lymph node metastases we used the classification is according to American Joint Committee on Cancer (AJCC) staging for axillary nodes in breast cancer[117].

- Macro-metastases = tumour greater than 2.0 mm in diameter.
- Micro-metastases = tumour cell aggregates between 0.2 and 2.0 mm in diameter.
- Isolated tumour cells =individual tumour cells or aggregates that are less than 0.2mm in diameter, usually detected by immunohistochemistry.
- Tumour absent – no tumour cells identified in H&E (or immunohistochemically, if applicable) stained sections.

3.3 STATISTICAL PLAN AND ANALYSIS

3.3.1 Paper I-III

3.3.1.1 Primary outcome

Statistical assumptions of the primary outcome (number of infrarenal paraaortic lymph nodes) were based on our previous experience that demonstrated a mean paraaortic lymph node yield of 16.4 lymph nodes for laparotomy, combined with benchmarking data from the Mayo clinic demonstrating a mean paraaortic lymph node yield of 17.4 with a standard deviation (SD) of 8 [11]. Minimum node count for systematic paraaortic lymphadenectomy has been reported as 10 [118], why a non-inferiority margin of 6 lymph nodes was chosen. A sample size of 47 patients in each group was rendered with a power of 95% and a one-sided alfa of 0.025. With an expected 20% dropout rate, 120 patients needed to be recruited. For analysis of mean difference, significance and confidence intervals in primary outcome, independent two-sided t-test was performed and the assumptions for the test was fulfilled. Mann Whitney U test was performed for unevenly distributed data. Frequency distributions between categorical variables were compared with Fisher's exact test. All P-values were two-sided and a P-value less than 0.05 was considered significant. All analysis is based on the per protocol (PP) group where complete staging was performed, except for proportion of patients with lymph node metastasis were the intention-to-treat group was analysed separately. Descriptive statistics were presented as median and range (minimum-maximum) or mean ±SD.

3.3.1.2 Secondary outcomes

The effect of known and potential risk factors on self-reported lymphoedema at 12-months after surgery was estimated and tested using linear regression models. Statistically significant ($p<0.05$) factors identified from the univariate analyses were all included in a final multivariate model. Results from these models are presented as mean differences together with 95% confidence intervals. Results from the multivariate analyses were confirmed by non-parametric bootstrap methods with 10.000 replicates [119]. Reported p-values refer to Wald tests. Agreement between self-reported lymphoedema (dichotomized to "not at all" and "any extent") at 12 months after surgery and lymphocele formation or ascites assessed by computed tomography, was evaluated using kappa statistics, a kappa (strength of agreement) of <0.20 was considered poor, 0.21-0.40 fair, 0.41-0.60 moderate, 0.61-0.80 good and 0.81-1.00 very good [120]. The proportion of women with any extent of reported lymphoedema before and at 12 months after surgery, as women who were admitted to hospital or experienced a serious adverse event between day 31-365 after surgery, were assessed and compared with Fisher's exact test. Data for the EORTC QLQ-C30/QLQ-EN24 was scored according to the EORTC QLQ-C30 manual, missing values were treated accordingly [121]. All scales were linearly transformed to range from 0 to 100. In the interpretation of the EORTC QLQ-C30/QLQ-EN24 scores a difference of >5 points were

considered clinically important for the patients, i.e. could be experienced by them [122]. Differences of 5-9 points were considered small, those of 10-19 moderate, and >20 large [123]. The effect of surgical modality on each of the scale scores at the 12-month assessment was evaluated using linear regression models including type of operation (laparotomy, robot assisted laparoscopic surgery) and baseline scale scores. Results from these models are presented as mean differences together with 95% confidence intervals. P-values from these models refer to Wald tests. A P-value of <0.05 was considered significant. No adjustment was made for multiple comparisons. For the EuroQoL EQ-5D-3L answers were dichotomised to "not at all" or "any extent" and comparisons at the different assessment time points were made without adjustment for baseline, proportions were compared with Fisher's exact test. For the EuroQol visual analogue scale (VAS), the median score at the assessment points by surgical modality was compared with Mann U Whitney test.

3.3.2 Paper IV

The analysis of sensitivity, false negative rates and negative predictive value was evaluated per patient with regards to the SNB algorithm and in mapped women only. As at least a full pelvic lymphadenectomy was performed in addition to the separate removal and analysis of SLNs. Each woman served as her own control in terms of overall pelvic node positivity. All women who underwent the planned procedure according to protocol were included in the analyses of primary outcome. All women injected with ICG tracer were included in the safety assessment.

As it has the highest probability of early termination under the efficacy hypothesis, the preferred statistical method was the Fleming two stage design for determination of sample size, interim analyses and decision to stop accrual based on sensitivity [124]. The null hypothesis that sensitivity was 85% was tested against a one-sided alternative with a desired sensitivity of at least 92.5%. The interim analysis was planned after 50 ICG mapped (at least one SLN-ICG) women with pelvic LNM were identified. This was continuously monitored and enrolment was stopped and interim analyses performed accordingly. Preliminary, this would require approximately 250 enrolled patients with an estimated 20% pelvic LNM rate. Enrolled women awaiting final histology when accrual was stopped were included in the study.

If the number of patients with pelvic LNM correctly identified by at least one ICG mapped SLN was equal to or lower than 43 the study would be stopped for futility. If the number of patients identified were equal to or higher than 48 the hypothesis of inefficacy could be rejected with no further enrolment. If the total number of success was between the lower and the upper cut-off points, the trial would continue by including an additional 69 patients with pelvic LNM. The hypothesis of inefficacy would be rejected if 107 or more patients with pelvic LNM were correctly identified by an ICG mapped SLN. This design yielded a type 1 error of 0.05 and a power of 0.8 when the true sensitivity is 92.5%. Exact 95% confidence intervals and sensitivity, false negative rates and negative predictive values are reported and estimated by proportions. Descriptive data was presented with numbers and percentage or median and range (minimum-maximum).

4 RESULTS

4.1 PAPER I-II

Between May 2013 and July 2016, 143 consecutive patients were assessed for eligibility to the RASHEC trial and 120 women were randomised, RALS (n=60) or LT (n=60).

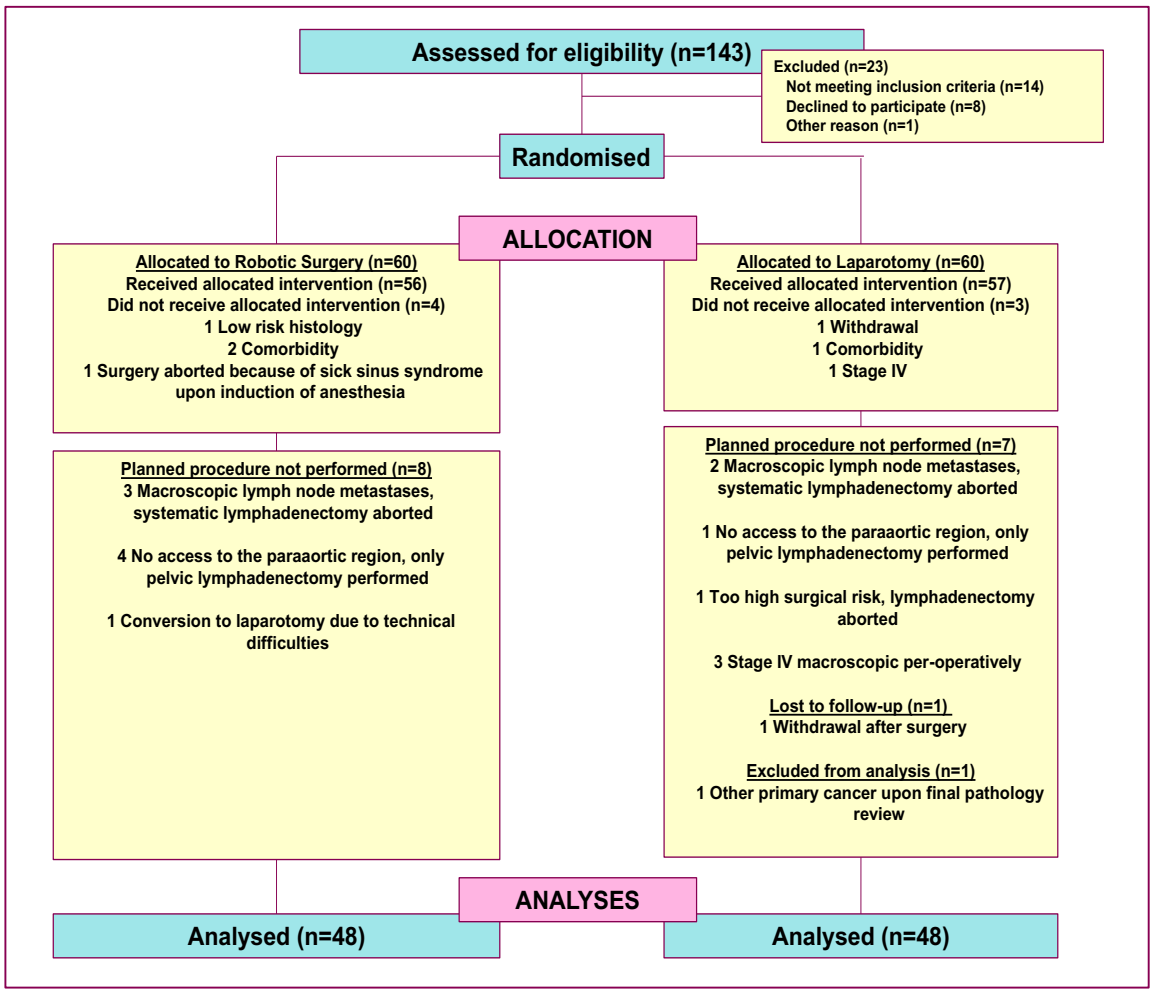

Figure 12. *Consort Flow Diagram RASHEC trial. Accrual between May 2013 through July 2016.*

As shown in Figure 12, four women in the RALS group and three in the LT group did not undergo the allocated procedure, leaving 113 patients in the intention-to treat group. Of the 56 patients in the RALS group, the procedure was aborted in 8 women (14.3%) due to gross lymph node metastases, technical difficulties gaining access to the paraaortic area or conversion to LT.

Table 1. Baseline demographics, clinical and pre-operative tumour characteristics of endometrial cancer patients by surgical technique, per protocol.

Characteristic	Laparotomy (n=48)	Robotic surgery (n=48)
Age, years		
Median	67	66
Range	52-75	39-75
BMI kg/m^2		
Median	27	26
Range	18-43	17-38
ECOG performance status, no. (%)		
0	47 (98)	45 (94)
1	1 (2)	3 (6)
Comorbidity, no. (%)		
Diabetes	4 (8)	2 (4)
Hypertension	18 (38)	21 (44)
Cardiovascular disease	5 (10)	4 (8)
Asthma	3 (6)	2 (4)
Previous malignancy*	8 (7)	4 (8)
Marital status, no. (%)		
Married or living with a partner	31 (65)	31 (65)
Has a partner but lives alone	3 (6)	3 (6)
Widow	1 (2)	1 (2)
Single	13 (27)	13 (27)
Level of education, no. (%)		
Elementary school	13 (27)	8 (17)
Secondary school	22 (46)	19 (40)
College/University	13 (27)	21 (44)
Employment status, no. (%)		
Student	0	0
Unemployed	0	1 (1)
Employed	17 (35)	17 (35)
Retired	31 (65)	30 (63)
Cigarette smoking		
Current smoker	9 (19)	3 (4)
Former smoker	15 (31)	14 (29)
Never smoker	24 (50)	31 (65)
Clinical FIGO stage, no. (%)		
I	43 (90)	42 (88)
II	5 (10)	6 (13)
Pre-operative histology, no. (%)		
Endometrioid	17 (38)	21 (44)
FIGO Grade 1	0	1 (2)
FIGO Grade 2	8 (17)	7 (15)
FIGO Grade 3	9 (20)	11 (24)
Non-Endometrioid	31 (65)	27 (56)
Serous	20 (42)	23 (48)
Clear cell	3 (6)	4 (8)
Carcinosarcoma	5 (10)	2 (4)
Other	3 (6)	0
Pre-operative myometrial invasion[4], no (%)		
<50%	33 (69)	29 (60)
≥50%	15 (31)	19 (40)

Abbreviations: BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics.
Range (minimum-maximum). * Ten patients with previous breast cancer, one with previous colorectal cancer and one with previous malignant melanoma.[1]Mann Whitney U test. [2]Fisher's exact test. [3]Students *t*-test.[4]Myometrial invasion estimated by magnetic resonance imaging or ultrasound.

In the LT group, the planned surgery was aborted per-operatively in 7 of 57 women (12.3%) due to gross lymph node metastasis, technical difficulties or disseminated disease (Fig. 12). One additional patient withdrew consent after surgery and the final pathology review of one patient revealed another primary cancer. 96 patients, evenly distributed between the surgery groups, were included in the per protocol analysis. A gynecologic expert pathologist reviewed 71% of the specimens in the LT group and 75% in the RALS group. 96 patients, evenly distributed between the surgery groups, were included in the per protocol analysis. Demographics, clinical and pre-operative tumour characteristics were well balanced between groups (Table 1).

4.1.1 Lymph nodes yield and metastases

There was no difference in mean number of para-aortic lymph nodes harvested up to the renal vein between RALS (20±9.6) and LT (22±11, p=0.45), see Table 2. Difference of means with a 95% confidence interval was within the non-inferiority margin for paraaortic lymph node count (-1.6, 95% CI -5.78 - 2.57) (Fig.13). Pelvic lymph node count was lower in the RALS vs LT group (22±8 vs. 28±10 p<0.001).

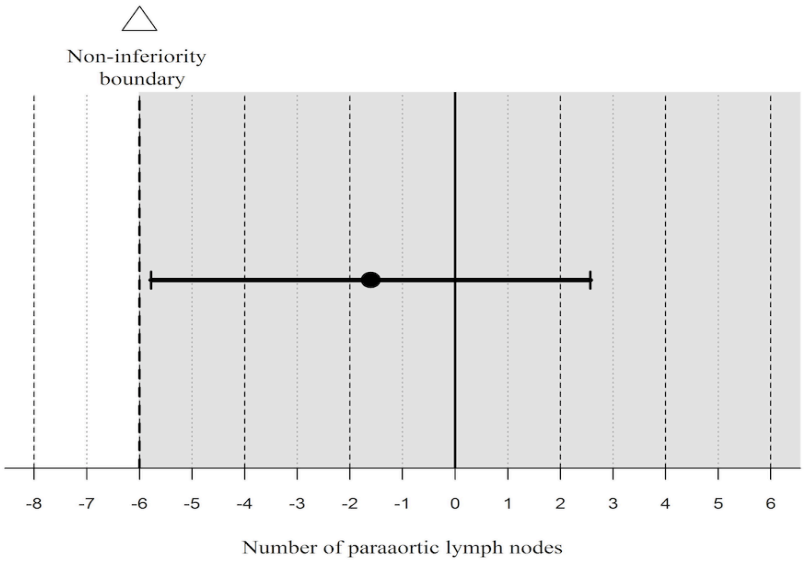

Figure 13. *Difference of means with 95% Confidence Interval in harvested paraaortic lymph nodes between robotic surgery and laparotomy*

In both the intention-to treat and per protocol analyses, the prevalence of lymph node metastasis was higher, albeit not significant, in the RALS group compared to LT (21% vs. 14% and 19% vs. 13% respectively).

If metastases were present, 47% were harboured in both the pelvis and paraaortic region, 33% only in the pelvis and 20% only in the paraaortic region, i.e. 3% of all women in the per protocol analysis had isolated paraaortic lymph node metastases. Paraaortic lymph node metastases were located above the inferior mesenteric artery (IMA) in 80% of the cases.

Table 2. Mean (±SD) number of lymph nodes harvested through systematic lymphadenectomy and the prevalence of lymph node metastases, by surgical modality.

Lymph node region	Laparotomy (n=48)	Robotic surgery (n=48)	*P*-value
	Mean (SD)	Mean (SD)	
Paraaortic region Above IMA[2] Below IMA[3]	22 (11) 13 (7) 10 (5)	20 (10) 12 (7) 9 (5)	0.45[1] 0.76[1] 0.52[1]
Pelvic region Left pelvis Right pelvis	28 (10) 14 (6) 14 (6)	22 (8) 10 (5) 12 (5)	<0.001[1] <0.05[1] <0.05[1]
Paraaortic and pelvic region	50 (19)	42 (16)	<0.001[1]
Lymph node metastases, n (%)	6 (13)	9 (19)	0.58[4]
Lymph node metastases ITT[5], n (%)	8 (14)	12 (21)	0.33[4]

Abbreviations: IMA, Inferior mesenteric artery; SD, standard deviation.
[1]Students *t*-test. [2]Above IMA is defined as the region between the renal vein and inferior mesenteric artery.[3]Below IMA is defined as the region between iliac bifurcation to the inferior mesenteric artery.[4]Fisher's exact test.
[5]Intention to treat analysis.

4.1.2 Peri- and postoperative outcomes and imaging

Peri- and postoperative short and long-term outcomes are shown in Table 3. There were no differences between the groups other than longer operation time, less total blood loss and shorter hospital stay in the RALS group. Moreover, there was no difference in lymphocyst formation although a non-significant difference was found in the anatomical distribution of lymphocysts, with a higher prevalence of paraaortic and lower prevalence of pelvic lymphocysts in the RALS group, though not significant (Table 3, Fig. 14).

None of the women had symptomatic lymphocysts requiring intervention.

In total, 22% (n=21) of the women had evidence of ascites at three months and 14% (n=13) at 12 months, with no statistically significant difference between RALS and LT (Table 3). One woman in the RALS group had symptomatic lymphatic ascites that required abdominal drainage on two occasions.

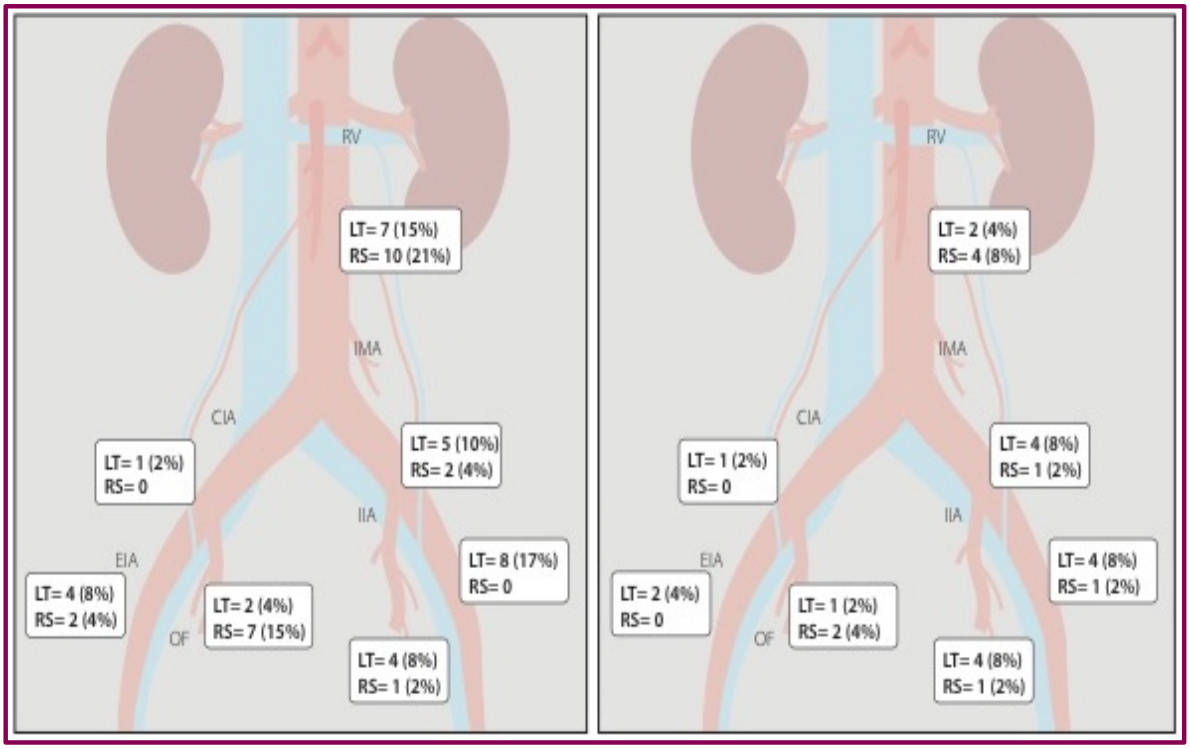

Figure 14. *Anatomic distribution of intraabdominal lymphocele formation after pelvic and infrarenal paraaortic lymphadenectomy. Left three months postsurgery right 12 months postsurgery. Abbreviations: LT, laparotomy; RS, robot assisted surgery; RV, renal vein; IMA, inferior mesenteric artery; CIA, common iliac artery; EIA, external iliac artery; OF, obturator fossa; ILA, internal iliac artery. Illustration by Mattias Karlén.*

Two women in the LT group had renal infarction (one right sided and one left sided) that progressed between CT at three and 12 months, but no intervention was needed and no impairment of the renal function was observed. Of nine women (9%) with findings suggestive of recurrence at 12 months, four had peritoneal carcinomatosis, one had multiple lung metastases, two had recurrence in multiple extra- and intraabdominal sites, one had vaginal cuff recurrence, and one had inter-aortocaval lymph node recurrence. There was no difference in the proportion recurrences (Table 3).

Table 3. Peri- and postoperative outcomes and findings upon imaging at three and twelve months by surgical modality

Outcome	Laparotomy (n=48)	Robotic surgery (n=48)	*P*-value
Operation time (minutes) Median Range	 187 109-300	 233 166-320	 <0.001[1]
Estimated total blood loss (mL) Median Range	 200 50-850	 78 20-300	 <0.001[2]
Intraoperative adverse events, no. (%)	4(8)	1 (2)	0.36[3]
Blood transfusions, no. (%)	1 (2)	0	1.0[3]
Admitted to intensive care unit, Planned or unplanned	0	0	
Length of hospital stay (days) Median Range	 5 4-9	 2 1-5	 <0.001[2]
Postoperative complications within 30 days[4], no. (%) I II IIIa IIIb IVa IVb V	 1 (2) 12 (25) 1 (2) 1 (2) 1 (2) 0 0	 3 (6) 5 (10) 2 (4) 1 (2) 0 0 0	0.36[3]
Readmissions within 30 days, no. (%)	5 (10)	3 (6)	0.82[3]
Postoperative day 31-365, no. (%) C-D grade ≥ 3 any reason Readmission any reason	 4 (8) 6 (13)	 7 (15) 7 (15)	 0.52[3] 1.00[3]
CT at three months, no. Lymphocysts 1st location 2nd location 3rd location Ascites Other Recurrence	48 23 (48) 7 (15) 1 (2) 7 (15) 4 (6) 0	48 18 (38) 4 (8) 0 14 (30) 3 (6) 0	 0.41[3] 0.52[3] 1.00[3] 0.14[3] 1.00[3]
CT at twelve months[5] Lymphocysts 1st location 2nd location 3rd location Ascites Other Recurrence	 13 (28) 3 (6) 0 8 (17) 3 (6) 5 (11)	 7 (15) 1 (2) 0 5 (10) 1 (2) 4 (8)	 0.14[3] 0.36[3] - 0.39[3] 0.36[3] 0.74[3]

Abbreviations: C-D, Clavien Dindo; CT, Computed Tomography of abdomen. Range (minimum-maximum). [1]Students *t*-test. [2]Mann Whitney U test. [3]Fisher's exact test. [4]According to Clavien-Dindo classification of surgical complications.[5] One patient in the laparotomy group died of endometrial cancer within 12 months and did not undergo CT at 12 months.

Between day 31-365 postoperatively, 13 patients were admitted to hospital. In the RALS group (n=7) two women had vaginal cuff rupture resulting in surgical intervention and were also admitted to hospital, one woman had fever and pelvic abscess resulting in intervention with drainage and admission to hospital, one woman fell and had rib-fractures and was admitted to hospital, one woman had a very early recurrence and was admitted to hospital and examined under anaesthesia with biopsy, one woman was diagnosed with breast cancer and admitted to hospital for surgical intervention and one woman had a disseminated recurrence resulting in admission to hospital for ChT and intervention with abdominal biopsy. In the LT arm one woman was admitted to hospital because of diverticulitis, one woman because of hypokalaemia, two women with recurrence of disease were admitted to hospital for placement of nephrostomy, one woman was admitted because of recurrence and required abdominal drainage of ascites and one woman was admitted for open heart surgery because of myxoma.

4.1.3 Self-reported lymphoedema

A total of 94 (98%) women completed the EORTC-QLQ-EN24 questionnaire at baseline and 94 (98%) at 12 months after surgery. At baseline, pre-surgery, 32% (n=15) in the LT group and 17% (n=8) in the RALS group reported any extent of swelling in one or both legs or feeling of heaviness in one or both legs (p= 0.10). The corresponding figures at 12 months after surgery was 61% (n=28) and 50% (n=24) (p=0.31). No significant difference in mean score of QLQ-EN24 items capturing LLL was found at 12 months after post-surgery, in relation to the number of pelvic or paraaortic lymph nodes, the delivery of chemo-radiotherapy or not, FIGO stage, the occurrence of co-morbidity, age or demographic characteristics (Table 4). A 10-point difference in mean score was found between BMI < 25 and those with > 30 but the difference was not statistically significant (p=0.13). The mean lymphoedema score and corresponding standard deviation at 12 months after surgery unadjusted for baseline score was 25 (28) for LT and 15 (20) for RALS. In univariate analysis, surgical modality ($p<0.05$) and abdominal drainage (p=0.02) were significantly associated with self-reported LLL at 12 months after surgery. However, neither variable was independently associated with self-reported LLL in the multivariable analysis (Table 4).

Table 4. Association between clinical factors and 12-month self-reported lower limb lymphoedema

			Univariate		*Multivariate*[1]	
Factor	**Level**	**Mean score at 12 months (SD)**	**MD (95% CI)**	**P**[2]	**MD (95% CI)**	**P**[2]
Operation	Open	25 (28)	Ref.		Ref.	
	Robot	15 (20)	-10 (-20 to 0)	<0.05	-6 (-14 to 3)	0.19
Drainage	No	26 (29)	Ref.		Ref.	
	Yes	14 (19)	-12 (-22 to -3)	0.02	-8 (-16 to 1)	0.09
Age (years)	<60	24 (30)	Ref.			
	60-69	20 (24)	-3 (-18 to 11)			
	70-75	18 (23)	-6 (-21 to 9)	0.41[3]		
Married/LWP	Yes	21 (25)	Ref			
	No	19 (24)	-2 (-13 to 8)	0.67		
Education	Elementary	23 (28)	Ref			
	Secondary	18 (22)	-5 (-18 to 9)			
	University	21 (27)	-2 (-16 to 12)	0.85[3]		
Work	At work	24 (28)	Ref			
	Retired	18 (23)	-6 (-17 to 4)	0.25		
BMI	<25	16 (20)	Ref			
	25-29	19 (24)	3 (-9 to 15)			
	>30	26 (31)	10 (-3 to 22)	0.13[3]		
Comorbidity	No	23 (27)	Ref			
	Yes	17 (22)	-6 (-16 to 4)	0.23		
FIGO Stage	I-II	19 (24)	Ref			
	III-IV	24 (28)	5 (-8 to 18)	0.42		
Chemo-radiation[4]	No	19 (24)	Ref.			
	Yes	22 (27)	2 (-10 to 15)	0.71		
Pelvic LND *number of nodes*	9-19	17 (21)				
	20-27	22 (24)	Ref. 5 (-8 to 17)			
	28-53	20 (29)	3 (-10 to 16)	0.62[3]		
Paraaortic LND *number of nodes*	2-15	20 (23)	Ref			
	16-24	20 (23)	-1 (-13 to 12)			
	25-51	20 (29)	-1 (-13 to 12)	0.94[3]		

Abbreviations: SD, standard deviation; MD, mean difference; CI, confidence interval; LWP, living with partner; BMI, body mass index; FIGO, International Federation of Gynecology and Obstetrics; BMI, body mass index.
[1]The multivariate model includes the statistically significant (p<0.05) variables Operation and Drainage from the univariate analysis as well as baseline lymphedema score. [2]Wald test.[3]Test for trend.[4]Chemotherapy followed by pelvic external beam radiation therapy

4.1.4 Health care costs

The total cost for RALS was significantly lower than LT. When excluding the investment cost for the daVinci system, the cost for RALS was even lower, Table 5.

Table 5. Estimated mean total cost per patient undergoing hysterectomy, bilateral salpingoophorectomy and systematic lymphadenectomy by surgical modality

	Laparotomy (n=48)	Robotic surgery (n=48)	p-value[1]
CPP* (SEK) Mean SD	140,000 SEK 21,892 SEK	120,861 SEK 27, 637 SEK	<0.001
CPP (Euro)[2] Mean SD	€16,807 €2,628	€14,509 €3,318	<0.001
CPP including investment cost for robot[3], SEK Mean SD	140,000 SEK 21,892 SEK	129,789 SEK 27,653 SEK	<0.05
CPP including investment cost for robot, Euro Mean SD	€16,807 €2,628	€15,581 €3,320	<0.05

Abbreviations: CPP, Cost Per Patient; SEK, Swedish Crowns; SD, Standard Deviation.
* The total cost per patients included all associated costs of ward care (e.g. staff, radiology, laboratory, medication) as well as costs related to activities performed in the operation theatre (all surgical instruments and draping included), postoperative care and pharmaceuticals.[1]Mann Whitney U test.[2]Exchange rate 2013, 1 Euro = 8.33 SEK. [4]Provided 350 procedures per year per robotic system.

4.2 PAPER III

Of the 113 women in the intention-to-treat group, the EORTC-QLQ-C30 and QLQ-EN24 was answered at baseline by 98% (n=55) of women in the RALS group and 96% (n=55) in the LT group. The corresponding figures at 12 months were 100% (n=56) and 81% (n=46), see Fig. 15.

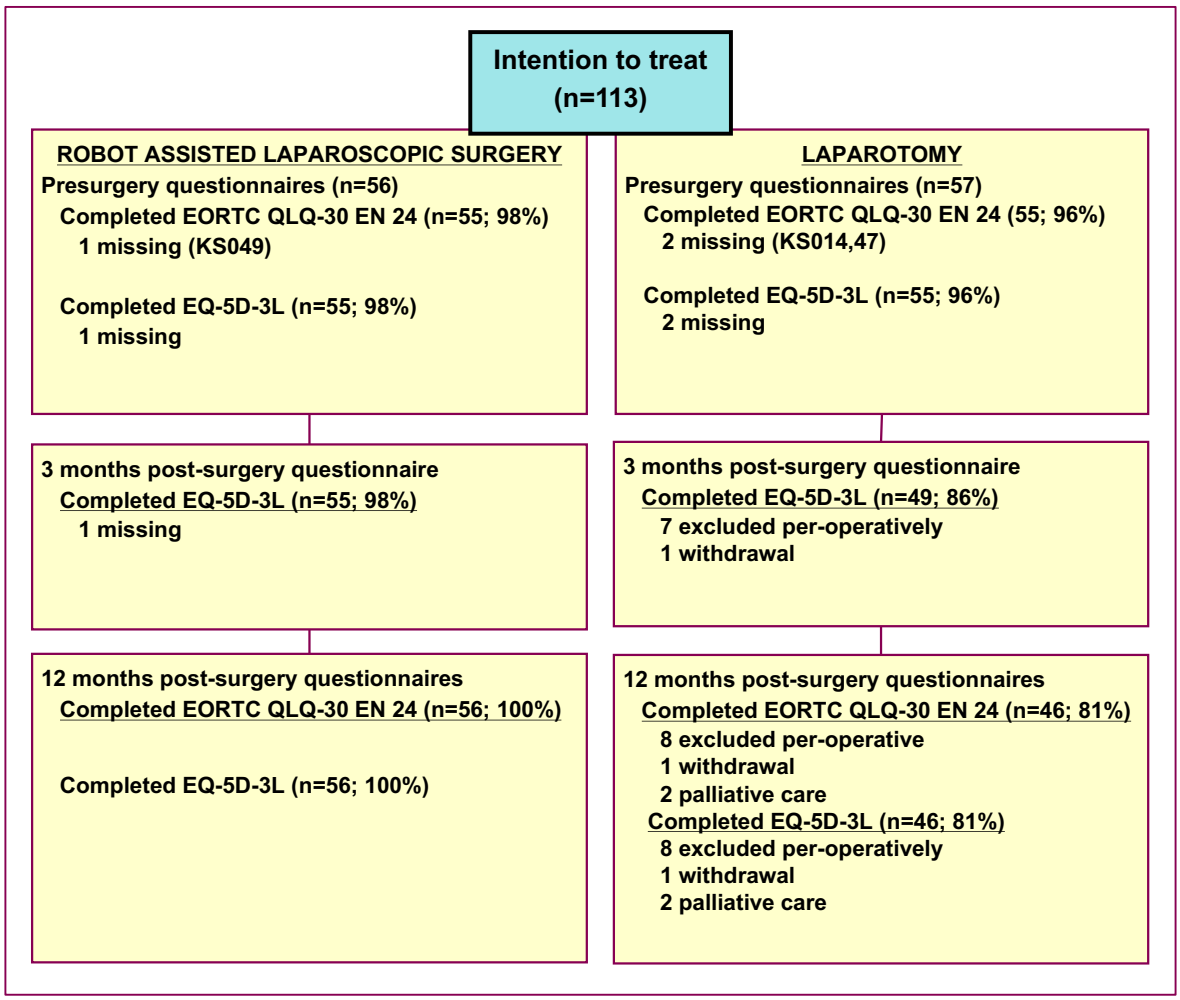

Figure 15. *HRQoL assessment diagram, intention-to-treat, n=113.*

Baseline characteristics/demographics, perioperative outcome did not differ substantially from the per protocol group, see Table 6. The majority of patients received adjuvant treatment, of which ChT was most commonly used (44% LT and 38% RALS). ChT followed by EBRT was delivered to 23% in LT group and 30% in RALS group. No patient received external beam radiotherapy only.

Table 6. Baseline demographics/characteristics and perioperative variables by surgical treatment, *intention-to-treat*

Characteristic	Laparotomy (n=57)	Robotic surgery (n=56)
Age, years, mean ±SD	66 ± 6	64 ± 9
BMI, mean ± SD	28 ± 6	28 ± 6
Weight, kg, mean ± SD	76 ± 15	75 ± 17
ECOG PS 0, no. (%)	55 (97)	53 (95)
Comorbidity no. (%)		
Diabetes	3 (5)	4 (7)
Hypertension	24 (43)	23 (40)
Cardiovascular disease	5 (9)	5 (9)
Asthma	4 (7)	4 (7)
Previous malignancy	6 (11)	9 (16)
Marital status, no. (%)		
Married or living with a partner	34 (60)	37 (66)
Widow	2 (4)	1 (2)
Single	17 (30)	15 (27)
Other	4 (7)	3(5)
Level of education, no. (%)		
Elementary school	16 (28)	9 (16)
Secondary school	27 (47)	24 (43)
College/University	14 (25)	23(41)
Employment status, no. (%)		
Employed	22 (39)	22 (39)
Unemployed	0	1 (2)
Retired	35 (61)	33 (59)
Adjuvant treatment, no. (%)		
Chemotherapy	25 (44)	21 (38)
Chemo-radiation	13 (23)	17 (30)
Operation time, minutes, mean ± SD	183 ± 50	229 ± 46
Postoperative complications grade ≥ 3[2], no. (%)	5 (9)	4 (7)

Abbreviations: SD, standard deviation; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; PS, performance status. [1]Randomly assigned patients, intention to treat.
[2]According to Clavien-Dindo Classification.

4.2.1 Health related quality of life

The results of the EORTC-QLQ-C30 are presented in Table 7. There was a statistically significant difference between the two surgical groups 12-months after surgery for "nausea and vomiting" in favour of LT (p=0.01) but the difference of 4 (95% CI 1 to 7) between the mean scores is not considered "clinically important" according to EORTC guidelines. Higher cognitive function was reported by the LT group compared to RALS, but the difference of -6 (95% CI -14 to 0, p=0.06) was statistically non-significant. However, a difference of -6 between the mean scores is according to EORTC guidelines "clinically important".

Table 7. EORTC QLQ-C30 and EN-24 scale scores at 12-months post-surgery by surgical modality[1]

	At 12 months Mean (SD)		*Controlling for baseline scores*	
EORTC QLQ-C30 scale	**Laparotomy**	**Robot-assisted surgery**	**MD[2] (95% CI)**	**P[3]**
Functional scales[4]				
Global health status / QoL	79 (18)	77 (18)	-1 (-7 to 6)	0.82
Physical functioning	87 (14)	87(14)	1 (-3 to 6)	0.56
Role functioning	88 (21)	86 (23)	1 (-8 to 9)	0.90
Emotional functioning	81(18)	82 (22)	0 (-7 to 7)	0.95
Cognitive functioning	88(15)	81 (21)	-6 (-14 to 0)	0.06
Social functioning	88 (16)	88 (18)	3 (-4 to 9)	0.42
Symptom scales/items[5]				
Fatigue	22 (20)	22 (17)	1 (-5 to 7)	0.81
Nausea and vomiting	1 (4)	5 (11)	4 (1 to 7)	0.01
Pain	14 (17)	13 (18)	-3 (-9 to 4)	0.40
Dyspnoea	20 (22)	20 (24)	3 (-6 to 11)	0.56
Insomnia	25 (22)	24 (24)	1 (-8 to 10)	0.80
Appetite loss	6 (19)	6 (13)	0 (-6 to 6)	0.99
Constipation	17 (24)	14 (23)	-1 (-9 to 8)	0.86
Diarrhoea	6 (13)	7 (16)	2 (-4 to 8)	0.61
Financial difficulties	5 (14)	4 (12)	-1 (-6 to 4)	0.65
QLQ-EN24				
Functional scales[4]				
Sexual interest	12 (16)	18 (22.0)	4 (-3 to 12)	0.26
Sexual activity	11 (17)	14 (22.8)	2 (-6 to 9)	0.68
Sexual enjoyment[6]	-	-	-	-
Symptom scales[5]				
Lymphoedema	25 (28)	16 (21)	**-6 (-14 to 3)**	0.20
Urological symptoms	18 (19)	15 (15)	-2 (-9 to 4)	0.43
Gastrointestinal symptoms	18 (18)	16 (15)	1 (-5 to 7)	0.80
Poor body image	13 (19)	19 (29)	**9 (-1 to 18)**	0.07
Sexual/vaginal problems[5]	-	-	-	-
Pain in back and pelvis	18 (24)	22 (26)	4 (-5 to 13)	0.33
Tingling/numbness	25 (31)	32 (30)	**6 (-6 to 19)**	0.32
Muscular pain	28 (26)	25 (25)	1 (-9 to 11)	0.83
Hair loss	13 (31)	17 (34)	**5 (-8 to 18)**	0.42
Taste change	3 (10)	7 (21)	**5 (-2 to 11)**	0.19

Abbreviations: EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core; QLQ-EN24, Endometrial cancer supplementary module; MD, mean difference; CI, confidence interval. Bold values indicate statistical significance or clinically important difference. [1]QLQ- 30: Number of patients included in the analyses range from 99 to 100 depending on the studied scale for QLQ-EN24 number of patients in the analyses range from 96-100 depending on studied scale. [2] Mean difference between surgical modality. [3]Walds test of significance.[4]Higher scores correspond to better functioning and global Quality of Life.[5]Higher scores correspond to a higher level of problems.[6]For the conditional scales Sexual enjoyment and Sexual/vaginal problems, where information was available for 11 patients only, mean scores are not reported.

The results of QLQ-EN24 are presented in Table 7. The largest difference was observed for body image, where patients in the RALS group reported poorer body image 9 (95% CI -1 to 18, p<0.07). However, no statistically significant difference was found between LT and RALS in any EN24 score.

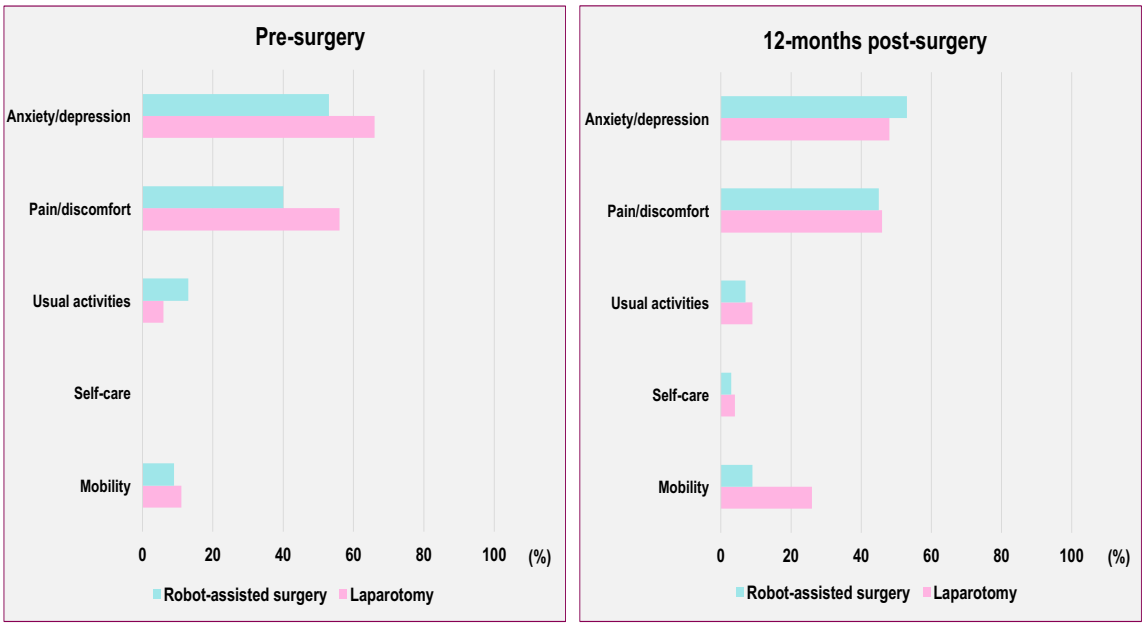

Figure 16. *Proportion women reporting any problems according to the EQ-5D-3L at the assessment time-points by to surgical modality.*

The EuroQol EQ-5D-3L questionnaire was answered at baseline by 98% (n=55) of women in the RALS group and 96% (n=55) in the LT group. Corresponding figures at 12 months were 100% (n=56) and 81% (n=46), respectively (Figure 1). At 12 months' post-surgery, a larger proportion of women in the LT group reported any extent of impairment of mobility (26% vs. 9%, p=0.03) as compared to the RALS group, but no other differences were observed, Fig. 16. There was no difference in the EQ-Visual Analogue Scale score between groups (80 in both groups, p=0.94), data not shown.

4.3 PAPER IV

Between June 2014 and May 2018, 355 women were assessed for eligibility. 275 women were enrolled and 261 underwent the planned procedure. One women was excluded due to other malignancy on final pathology and three women (none with LNM) were operated by a non-accredited surgeon and excluded due to protocol violation. Thus, 257 patients were analysed, see flow diagram in Figure 17.

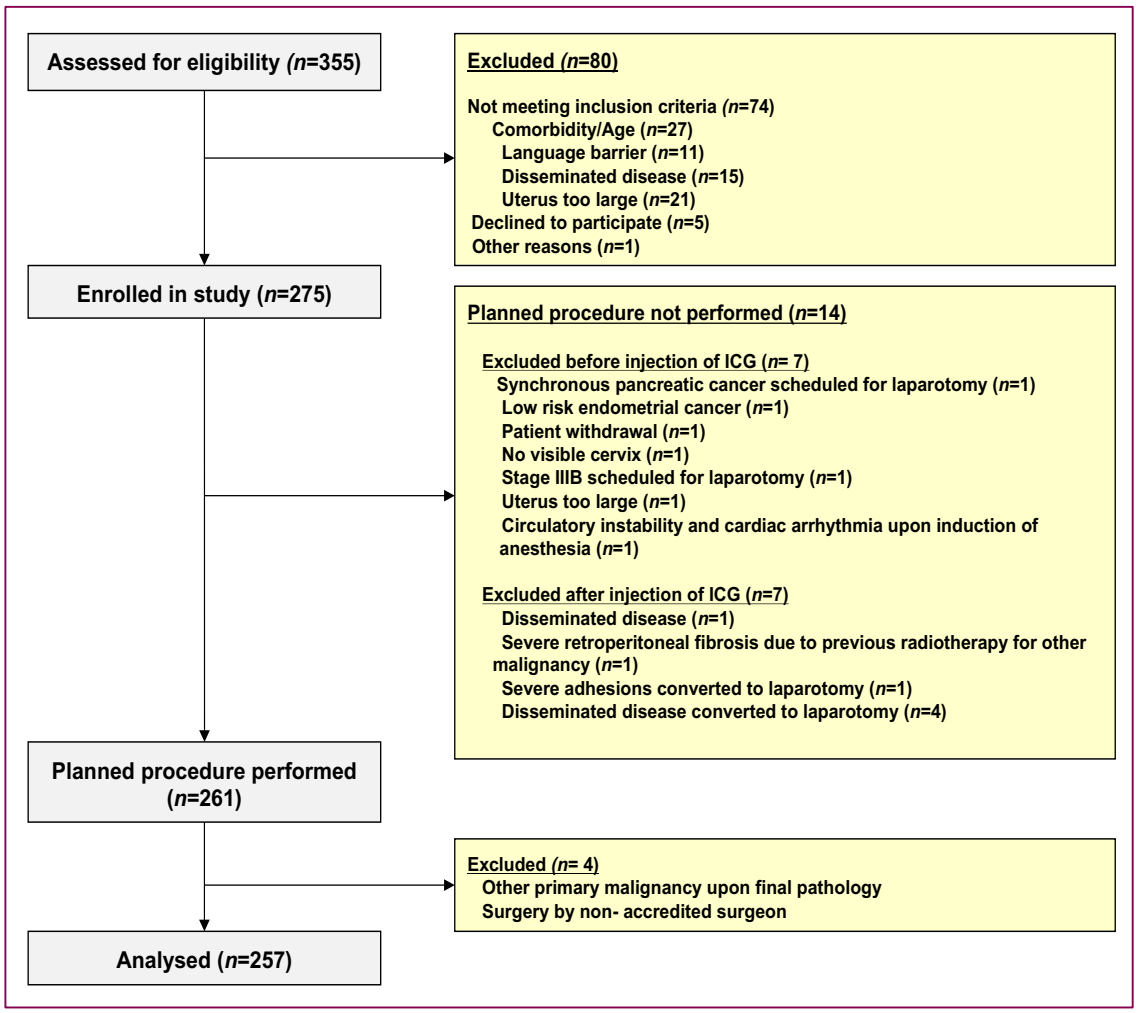

Figure 17. *Flow diagram, SHREC study. Accrual June 2014 through May 2018*

Median age was 71 (range 44-90), body mass index 27 kg/m^2 (range 17-47) and operation time 224 minutes (range 115-440). All participants had HREC by preoperative assessment with 86% (n=220) remaining HREC upon final histology. The majority of patients had endometrioid subtype (64%).

4.3.1 Sensitivity and negative predictive value

The overall pelvic SNB algorithm had a sensitivity of 100% (95% CI 92-100) and a negative predictive value of 100% (95% CI 98-100), see Table 8. In successfully mapped women, the sensitivity of the sentinel lymph node specimen was 98% (95% CI 89-100) and a negative predictive value of 100% (95% CI 97-100).

Table 8. 2x2 table for sensitivity and NPV of the pelvic SNB algorithm [1,2]

	True positive	True negative	Total
Positive metastasis by SNB algorithm	54	0	54
Negative metastasis by SNB algorithm	0	201	201
Total	54	201	255

Abbreviations: NVP, negative predictive value; SNB, sentinel node biopsy.[1] *Including side specific lymphadenectomy in case of non-display, resection of macroscopic lymph nodes suspicious for metastases and reinjection of tracer in case of non-display.*[2]*The two women with isolated paraaortic lymph node metastases not included in the analysis, since the algorithm exclusively evaluates pelvic lymph node detection.*

4.3.2 Detection rate of SLN, extent of lymphadenectomy and lymph node yield

Prior to and after reinjection the overall mapping rate (at least one ICG positive SLN) was 95% and 98%, and the bilateral mapping rate was 83% and 94% respectively.

All 257 women underwent pelvic SLN mapping and a full pelvic lymphadenectomy. IRPALND was performed in 208 (81%) women and in 9 (4%) women the paraaortic lymphadenectomy was restricted to the level of the inferior mesenteric artery. The median number of removed pelvic nodes was 29 (range 8-75) and paraaortic nodes 12 (range 2-51). The median number of type 1-2 SLNs was 4 (range 1-7), see Table 9.

Table 9. Extent of LND, node count, proportion metastases and successfully mapped women[1]

Variable	n=257
Surgical lymph node assessment, no. (%)	
SLN + Pelvic LND	40 (16)
SLN + Pelvic + inframesenteric paraaortic LND	9 (4)
SLN + Pelvic + infrarenal paraaortic LND	208 (81)
Detection of pelvic SLN, no. (%)	
First injection of ICG	
Unilateral	244 (95)
Bilateral	213 (83)
Reinjection of ICG	
Unilateral	252 (98)
Bilateral	242 (94)
Sentinel lymph node yield	
Median	4
Min-Max	1-7
Lymph node metastases, no. (%)	56 (22)
Isolated paraaortic lymph node metastases[2], no. (%)	2 (1)
Isolated pre-sacral lymph node metastases, no. (%)	1 (0)
Isolated parametrial lymph node metastases, no. (%)	0 (0)
Pelvic lymph node yield	
Median	29
Min-Max	8-75
Paraaortic lymph node yield[2]	
Median	12
Min-Max	2-51

Abbreviations; LND, lymph node dissection; SLN, sentinel lymph node; ICG, indocyanine green. [1]Analysed women only. [2]Among the 217 women subjected to paraaortic LND.

4.3.3 Lymph node metastases

56 of the 257 in the per protocol analysis had lymph node metastases. Two women (1%) had isolated paraaortic LNMs. A total of 54 women had pelvic LNM. In one of 54 women mapping failed. Of the remaining 53 women who were successfully mapped, 52 were accurately diagnosed with pelvic LNM in their sentinel lymph node with one having a false negative sentinel lymph node. However, both the non-mapped woman and the woman with a false negative sentinel node were identified by the algorithm through resection of suspicious macroscopic pelvic lymph node metastases (SLN macro)

Nineteen of the 52 women (36%) with ICG positive metastatic SLNs had micro-metastases (MM) or isolated tumor cells (ITC). In three of the 23 women (13%) with paraaortic LNM, pelvic LNM was restricted to SLNs with only MM or ITC.

Eleven women (20% of node positive patients) had pre-sacral metastases, 27% of these did not map along the LPP. One woman had an isolated pre-sacral metastasis. Pre-sacral metastases were more common in women with a non-endometrioid histology (36% compared to 10%). 108 patients (42%) had lymph nodes in the resected parametria, eight of these women (7%) had metastatic parametrial nodes. None had isolated metastatic parametrial nodes.

Of the patients with LREC upon final histopathology, three (8%) had pelvic LNM. 26% of women with HREC upon final histopathology (n=220) had lymph node metastases.

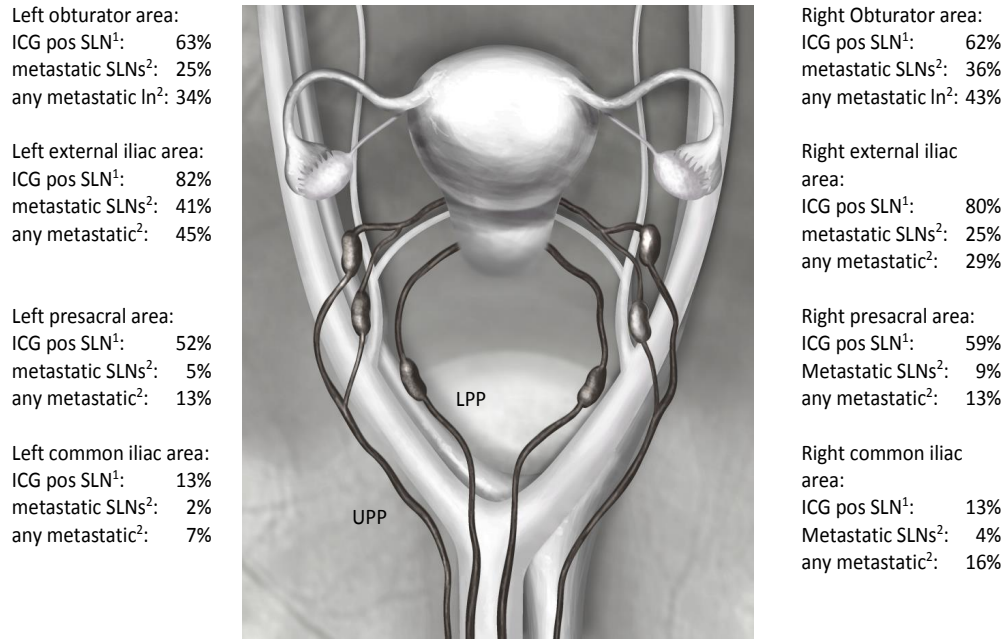

Figure 18. *Schematic overview of the pelvic uterine lymphatic pathways with typical localisation and proportion ICG positive and metastatic sentinel lymph nodes per lymph compartment. Percentages refer to; [1]the total number of women, [2]node-postive women; it is possible to have more than one ICG positive or metastatic sentinel lymph node. Left parametria, 18/56 women had lymph nodes of which four with metastasis. Right parametria, 22/56 women had lymph nodes of which five with metastasis (Data not shown). Abbreviations: UPP, upper paracervical pathway; LPP, lower paracervical pathway.*

The anatomic location of lymph node metastases and sentinel lymph nodes are presented in Fig. 18.

4.3.4 Perioperative adverse events and postoperative complications

All women in whom ICG was injected (*n*=268) were analysed for adverse events and postoperative complications, see Table 10. Five women were converted to laparotomy due to disseminated disease (*n*=4) or intraabdominal adhesions (*n*=1) following ICG injection but prior to docking the robot. No adverse events occurred during injection of ICG or during the sentinel node procedure per se. In total, eight (3%) patients experienced a per-operative complication.

Table 10. Perioperative adverse events and postoperative complications[1]

Variable	n=268
Adverse Events, no. (%)	
Before docking the robot[2]	9 (4)
Conversions to laparotomy	4 (1)
Disseminated disease	1 (0)
Intraabdominal severe adhesions	1 (0)
Trendelenburg position not tolerated	3 (1)
Bleeding during surgery	
During Sentinel node dissection	
None observed	
During completion PLND ± PALND	8 (3)
Large vessel injury	6 (2)
Nerve injury	1 (0)
Bowel injury	1(0)
During hysterectomy	
None observed	0
Postoperative 30 day complications[3], no. (%)	
I	36 (13)
II	28 (10)
IIIa	14 (5)
IIIb	5 (2)
IVa	1(0)
IVb	1(0)
Readmissions to hospital[4], no. (%)	9 (3)

Abbreviations: PLND, pelvic lymph node dissection; PALND, paraaortic lymph node dissection.[1] All women enrolled in whom ICG was injected in the uterine cervix (intention to treat.) [2]During injection of ICG, insufflation, port placement and conversions to laparotomy. [3]According to the Clavien Dindo classification. [4]Within 30 days after surgery.

Eighty-five (32%) women had a postoperative complication within 30 days of after surgery (Table 10). Nine women (3%) experienced a serious adverse event (SAE), three during and six after surgery. Five of the six postoperative SAEs were categorized as such due to prolonged hospital stay (> 5 days). The readmission and reoperation rate within 30 days after surgery was 3% and 7% respectively.

5 DISCUSSION

5.1 PAPER I-III

The studies from the RASHEC trial demonstrate that robot-assisted laparoscopic surgery is non-inferior to laparotomy in harvesting paraaortic lymph nodes both above and below the inferior mesenteric artery. Moreover, that RALS provides lower health care costs. Furthermore, our results suggest that there are no differences between LT and RALS in short- or long term complications, lymphatic side effects and HRQoL.

The current surgical management of endometrial cancer is largely based on the patterns of lymphatic dissemination described in a prospective study from the Mayo clinic [11]. A large proportion of paraaortic metastases was found to be located between the renal vein and the IMA and the former practice of limiting the PALND to the IMA was proven insufficient. The lack of international consensus regarding lymph node count as a quality indicator for comprehensive staging is illustrated by the vast discrepancies between the ESMO-ESGO-ESTRO guidelines and the benchmarking data from the Mayo clinic. In the former, a minimum number of 10 nodes *in total* is required whereas the latter defines comprehensive staging to include at least 22 pelvic and 10 paraaortic lymph nodes [118]. Increasing the number of harvested lymph nodes or the extent of lymphadenectomy may have clinical implications with improved survival in patients with high-risk disease [24,125-127]. Whether this is suggestive of a therapeutic effect of lymphadenectomy or merely represents a more accurate staging is unknown. In our study, the paraaortic lymph node count as well as the proportion of metastases in the ITT analysis was consistent with previous reports [128]. Furthermore, the locations of lymph node metastases were also coherent with previous data and reproduces previously described patterns of lymphatic dissemination [11]. Interestingly, we found a significantly lower pelvic node count after RALS. These data corroborate with recent findings suggesting that minimally invasive surgery may result in a lower number of harvested pelvic lymph nodes [129]. However, the mean number of pelvic nodes after RALS met the quality criteria suggested by the Mayo clinic [118].

RALS was associated with fewer per- and postoperative complications than LT, albeit not statistically significant. More importantly, the number of major postoperative complications (Clavien-Dindo > 2) was the same between the groups, contrary to previous reports [130,131]. Comparing complications between studies poses difficulties since the grading systems, definitions and cohort sizes vary considerably. In a relatively recently published systematic review comparing RALS with LT for endometrial cancer, the majority of included studies showed no significant differences in perioperative complications [29].

The proportion of women with long-term adverse events and admissions to hospital between one and 12 months after surgery, for any reason, did not differ. In total, two women were diagnosed with unilateral renal infarction by computed tomography after LT,

though without impairment of renal function. This unexpected and potentially serious complication would have gone unnoticed without follow-up imaging as part of the study protocol. The risk of "silent" injury to the renal arteries during IRPALND is unknown, but experiences from retroperitoneal lymph node dissection in testicular cancer patients, suggest a 1.4-4% risk of per-operative renal artery injury [132,133].

Since consensus on standardized measures and definition of LLL are lacking, dispersion of reported incidence and prevalence estimates after endometrial cancer treatment is wide, ranging between 5-38% and 0-50% respectively [33-35,39,40]. After IRPALND, the proportion of patients with LLL, has been reported to 18% and 37% for robot-assisted surgery and LT respectively [41,42]. Proportions reported in our study were higher with 54% of all women reporting any extent of LLL symptoms 12 months after surgery. In contrast to our study, lymphoedema assessment in the study by Geppert et al was performed by a physiotherapist using the CTC version 3.0 classification [41]. It is widely accepted that patient-reported outcomes differ from estimations by health care providers [134-136]. In line with the recommendation from GCIG we used a validated questionnaire, in this case the EORTC QLQ-EN24, to capture the occurrence of symptoms indicating lower limb lymphoedema [137]. In a Swedish study by Bergmark et al, heavy or swollen legs and/or lower abdomen were reported at least occasionally by 39% to 41% of patients 5 years after radical hysterectomy for cervical cancer [138]. In our study of endometrial cancer patients, the median age and rate of comorbidities was higher compared to cervical cancer patients in Sweden, which may have contributed to a higher prevalence of reported symptoms. The uneven distribution of women reporting any extent of LLL at baseline despite randomisation may be attributed to chance and might have been balanced if the sample size of the study was larger.

Risk factors associated with LLL include lymphadenectomy, number of harvested pelvic lymph nodes, external beam radiotherapy and obesity [33-38]. Clearly, surgical disruption of lymphatic channels or radiation-induced fibrosis constitute reasonable causes of treatment related lymphoedema. However, the heterogeneity in reported symptoms from treated patients illustrate the complexity of the underlying pathophysiology. Indeed, obese women may suffer from lymphoedema without prior surgery or radiation and obesity may aggravate therapy-induced symptoms [139,140].

None of the mentioned risk-factors were associated with lymphoedema in our study. Paraaortic lymph node yield had no association with LLL with the same mean lymphoedema score at 12 months regardless of lymph node yield, suggesting that the paraaortic lymphadenectomy per se does not add to LLL. Furthermore, abdominal drainage was not associated with a decrease in self-reported LLL.

It has been suggested that minimally invasive surgery (MIS) significantly decreases the incidence of lymphocysts identified by ultrasound after lymphadenectomy [43]. In our study, lymphocyst formation (or ascites) on computed tomography of abdomen did not differ between surgical modality.

Interestingly, paraaortic lymphocysts were more prevalent after RALS in contrast to pelvic lymphocyst formation. Compared to laparotomy, RALS requires a smaller incision of the paraaortic peritoneum to prevent the bowels from obstructing the surgical field. This may result in quicker healing of the peritoneum and may explain the larger number of paraaortic lymphocysts. However, the frequency of observed lymphocysts or ascites had no clinical implication and no agreement with lymphoedema score 12 months after surgery.

Two previous trials, that included mandatory comprehensive surgical staging comparing surgical modalities in relation to HRQoL outcomes, have been conducted. The GOG LAP2 trial, where pelvic and inframesenteric paraaortic lymphadenectomy was performed, assessed HRQoL by the Functional Assessment of Cancer Therapy Scale-General (FACT-G) questionnaire [49,141]. The only significant difference in favour of laparoscopy at 6 months' follow-up was body image, though no clinically important difference (CID) was met [48]. In the study by Zullo et al, where pelvic lymphadenectomy was mandatory and paraaortic lymphadenectomy performed in 7%, the Short Form Health Survey 36 (SF-36) questionnaire was used. The authors observed favourable outcomes for laparoscopy in all domains of the questionnaire at 6 months, but measures of clinically important differences were not reported [50,142].

Based on the previous result of these studies, we expected to find significantly better HRQoL among women treated with RALS in our study. However, the only statistically significant difference in mean scores was observed in favour of LT for nausea/vomiting. The mean difference was small and did not meet CID [123]. We therefore find it unlikely that this finding has any relevance for the treated women. Cognitive impairment have been reported after surgery, though the underlying mechanisms are not fully understood [143] .

Although not statistically significant, a small clinically important difference in cognitive functioning in favour of LT was observed in the current trial. The Trendelenburg position required for robot assisted pelvic surgery might be associated with cerebral hypoxia, though reports are scarce [144]. Furthermore, it is well known that ChT may result in cognitive impairment [145]. Whether this finding has any relevance must be further explored in larger trials.

Given that the only difference in HRQoL reported in the LAP2 trial was superior body image after MIS, we were surprised to find similar mean scores in both treatment arms in the current trial. The larger incision required by laparotomy to access the infrarenal area should reasonably lead to a poorer body image in the LT arm. On the contrary, a CID was apparent in favour of LT, although not statistically significant. Several studies support the results from the LAP2 trial, reporting better cosmetic satisfaction after MIS. Higher level of satisfaction with scar cosmesis does not, however, necessarily translate to better body image [146-149].

It could be argued that a full midline scar is a constant visual reminder of the patient's cancer diagnosis, which conceptualizes a different frame of reference that remains in the long-term.

Furthermore, the mean age in our study could reflect a different attitude and acceptance in elderly women. Finally, cultural differences between countries in which the studies were conducted may affect the response [48,80].

Statistically significantly fewer women in the RALS reported any extent of mobility impairment in the EuroQoL EQ5D-3L one year after surgery as compared to LT. Few women reported, however, any extent of impairment (LT n= 12, RALS n=9). In addition, no between group differences were found for the other four questions including the EQ5D VAS score. The results should be interpreted cautiously, especially since no adjustments for baseline score were made.

Possible explanations for the observed differences in HRQoL between the current and previous trials include the duration of follow-up and the extent of surgical staging. In both the LAP2 and the trial by Zullo et al, 6 months' follow-up were used whereas our long-term assessment encompasses the end of adjuvant treatment, with follow up 12 months after surgery. It is possible that the favourable HRQoL outcomes reported in previous trial would have been less apparent 6 months later. Whether the more extensive staging procedure applied in the current study mitigates the effect of minimally invasive access on HRQoL remains speculative.

A major concern regarding RALS is the associated costs for acquisition, maintenance and single-use equipment. Several studied have identified robot-assisted surgery as a major cost driver although cost efficiency may be achieved in high-volume settings [91]. In comparison with conventional laparoscopy, RALS is generally considered more expensive but effects of the initial learning curve may have biased early reports [150,151]. In spite of higher procedural costs and longer operation time, we demonstrate a significantly lower cost after RALS, even when capital costs were included. The saving is mainly due to the considerably shorter length of hospital stay but other factors e.g. less need for postoperative analgesia, contributed to the result.

As most women in the RASHEC trial were retired, the cost for absence from work and sick-leave, which would undoubtedly be in favour of RALS, is not included in the analysis. Moreover, in the setting of the RASHEC trial, all women who were subjected to laparotomy regardless of diagnoses, were offered in-patient post-operative rehabilitation at a health care facility outside the hospital. Neither these costs that most certainly would be lower for RALS, were included in the analysis. Nonetheless, the finding should be interpreted with caution. It is important to stress that the cost savings was achieved in a high-volume institution with highly experienced surgeons and the generalizability of these results can be questioned.

In the intention-to-treat analysis, four women randomised to RALS did not receive planned procedure due to inability to access the paraaortic surgical field. In addition, one patient was converted to laparotomy. Consequently, 9% (n=5) of patients did not receive planned surgical

procedure because of inherent limitations of RALS. However, this proportion is considerably lower than the 25% reported for traditional laparoscopy[141]. Conversion to LT was low (1.8%) and supports the notion that RALS entails less conversion than conventional laparoscopy[152]

5.2 PAPER IV

The SNB algorithm applied in the SHREC trial demonstrate a sensitivity to identify pelvic LNM of 100% with a technical bilateral success rate exceeding 90%. No adverse events related to the sentinel node procedure per se were recorded.

The sensitivity and bilateral mapping rate demonstrated in the SHREC trial is higher than previously reported. The pooled bilateral SLN detection in a recent systematic review was only 61% whereas the sensitivity was 94% [153]. In order to replace systematic staging in EC, the technical success (i.e. bilateral mapping) of the SNB algorithm must ensure a low rate of lymphadenectomies. In the SHREC trial, a total of four pelvic lymphatic pathways were evaluated as previously described [61]. Furthermore, the total dose and number of injection sites in the cervix was higher than in the FIRES trial. Moreover, reinjection of ICG was permitted in case of uni- or bilateral failure to map the lymphatic pathways. The latter resulted in an increase of successful mappings from 83% to 94% and only 6% of the study population would have required additional lymphadenectomy if the SNB algorithm had been standard of care. Even in the absence of reinjections, a remarkably high bilateral mapping was observed.

This finding suggests the need of a strict surgical and anatomical algorithm, albeit surgical proficiency may have contributed to the results.

Contrary to other studies, the SHREC trial only considered pelvic disease in the SNB algorithm. As a result, the two women with isolated paraaortic metastases were not included in the analysis. A SLN was defined as the juxtauterine node in the pelvic lymph node basins. Consequently, a paraaortic SLN would require the complete absence of nodes along the mapped pathways in the pelvis. Given that more than 250 women were mapped in the SHREC trial, we find it unlikely that paraaortic SLNs can be detected by the current SNB algorithm. Whether peri-tumoural injection of tracer would enable identification of the afferent lymphatic pathways along the infundibulo-pelvic (IP) ligament with associated paraaortic SLNs remains to be demonstrated. Clearly, the inability to detect extra-pelvic disease limits the diagnostic accuracy of the pelvic SNB algorithm. However, the pelvic SNB algorithm is supported by the lower rate of isolated paraaortic metastases than previously reported [11,17,154]. We speculate that the high mapping rate and, as suggested by other authors, the use of ultrastaging accounts for this finding. [72,73]. Indeed, ultrastaging identified low-volume disease (Micro-metastases or ITC) in 13% of SLNs associated with paraaortic metastases, decreasing the rate of what would have been considered isolated paraaortic metastases from 2% to 1%. Consequently, low-volume disease in pelvic SLNs may be a risk factor for paraaortic LNM. Furthermore, only 0.4% had isolated presacral LNM, suggesting that the identification of the LPP can be omitted, which further simplifies the procedure.

There were no adverse events related to injection of ICG or the sentinel lymph node procedure in contrast to 3% during completion lymphadenectomy. This emphasizes the potential for reducing morbidity with a SLN concept compared to a full pelvic and paraaortic lymphadenectomy. The rate of postoperative more serious complications (Clavien Dindo > II) within 30-days was 8% and consistent with previous reports [154].

The strength of this trial includes the prospective design, with consecutive recruitment of women within a publicly available health care system. Moreover, only women with HREC and thus a higher prevalence of LNM were included and the majority were subjected to a full staging procedure including IRPALND. Furthermore, the definition of the surgical procedure was exact and performed by five accredited surgeons within two tertiary referral centres resulting in a high internal validity. All surgeries in the SHREC trial were performed by highly experienced surgeons and the generalizability of the results can be questioned. The study was also limited by differences in histologic assessment of excised lymph nodes where ultra-staging was performed on sentinel node specimens only.

The SHREC trial is the largest trial investigating the SNB algorithm in HREC, corroborating the results from the FIRES trial where the majority of women had LREC. The results from the SHREC trial represent a paradigm shift in surgical staging of high-risk endometrial cancer. With a satisfactory detection rate and a complete sensitivity to detect pelvic lymph node metastases, the sentinel node algorithm should replace lymphadenectomy in women with high-risk endometrial cancer. Future trials should address the optimal management of women with SLN positive disease.

6 METHODOLOGICAL CONSIDERATION

6.1 PAPER I-III

6.1.1 The Randomised Controlled Trial (RCT)

The RCT is the most reliable scientific method of comparison, primarily because of the randomisation that minimises risk of accidental bias and confounding. Weaknesses include that a RCT cannot compensate for confounding during follow up and imbalances between groups that can still occur by chance (sample size important). The RCT may have different hypotheses.

The aim of the superiority trial is to establish if one treatment is better than another or placebo. The null hypothesis (H_0) is that there is no difference between the two treatment arms whereas the alternative hypothesis (H_A) states that there is a difference between the experimental group and control. If the new treatment fails to be superior, the conclusion that the treatments are equal or the interventional treatment is worse cannot be drawn (if a predefined non-inferiority margin has not been decided in the study protocol) [155].

The non-inferiority trial aims to establish if a new treatment is as good as an existing, motivated by that there are other advantages of the new treatment (e.g. toxicity profile, complications, health care costs). The H_0 of the non-inferiority trial states that the new treatment is inferior or worse than the control by more than the chosen non-inferiority margin (Δ), see Fig. 19. The H_A states that the new treatment is inferior to the control treatment by less than Δ. For this reason, it is of utmost importance that the chosen non-inferiority margin is relevant, carefully considered and motivated for the basic validity of the trial design [156].

The statistical assumption of a non-inferiority trial is often more difficult to understand than the relatively straightforward assumptions of the superiority trial. In addition, both superiority and inferiority can be demonstrated with a non-inferiority design. However, if the upper and lower bounds of the confidence interval crosses the Δ and 0 (or 1 depending on measure of comparison) no other conclusion can be drawn other than that the intervention has not demonstrated a non-inferiority[157].

The non-inferiority margin of the RASHEC trial was based on previous literature on reported lymph node yield and from a pilot study. Nonetheless, lymph node count is not universally defined. There are no anatomic studies on mean number of infrarenal lymph nodes in the human female and lymph node count is very much at the discretion of the pathologist's exactitude.

The chosen non-inferiority margin which forms the absolute basis of the trial, can thus be criticised.

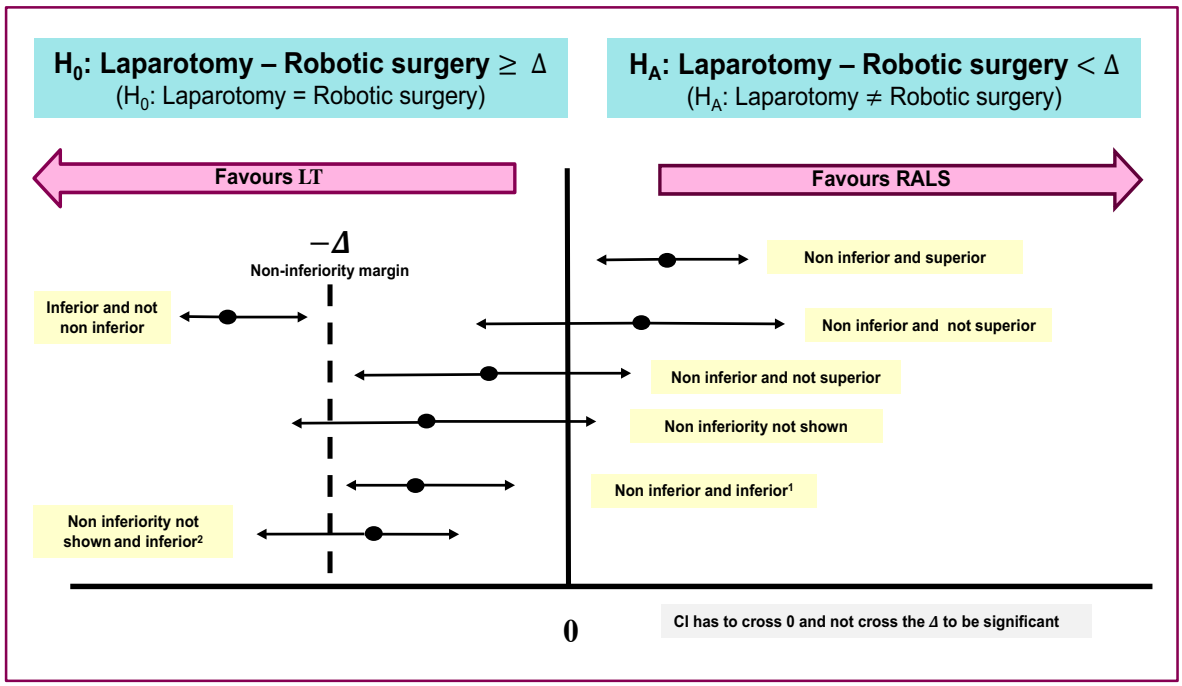

Figure 19. *Different possible outcomes with point estimates and accompanying CI that can be interpreted in a non-inferiority trial. Blue boxes with bold letters are the hypothesis of the RASHEC trial: the H_0 states that the difference of means between number of paraaortic lymph nodes between LT and RALS is higher or equal to the chosen non-inferiority margin of -6 paraaortic lymph nodes. The H_A states that the mean difference in number of paraaortic lymphnodes between LT and RALS is less than the chosen non-inferiority margin of -6 lymph nodes. In brackets are the corresponding hypothesis of a superiority trial.*

Abbreviations; H_0, null hypothesis; H_A, alternative hypothesis; LT, laparotomy; RALS, robot-assisted surgery; CI, confidence interval.

[1]The CI indicates non-inferiority since Δ is not included, but RALS is here significantly worse than LT why inferior. [2]The CI is inconclusive and the true difference between RALS and LT might less than Δ, but RALS is significantly worse than LT why inferior.

6.1.1.1 Randomisation

The RASHEC trial was open labelled, meaning that both the participant and treating surgeon knew which intervention the participant was allocated to after randomisation. This can result in selection bias (see 6.1.1.4.1, Selection bias), e.g. if a patient would withdraw consent because of the allocated treatment.

It would have been possible to mask the patient, at least for a couple of weeks postoperatively, if all other aspects of surgery would be constructed for this reason (e.g. sham robot theatre, sham epidural analgesia, sham dressings etc.). However, the implementation of such a strategy in

clinical practice would not be realistic. For obvious reasons, the surgeon could not be masked as to which treatment the participant would receive.

To ensure a reasonably even distribution of RALS or LT, the only practical randomisation technique that enabled the RASHEC trial to be conducted was block-randomisation.

Each patient drew a sealed envelope at the out-patient clinic. Ideally this should have been performed at an external and independent entity without any other direct contact with the study participants. One could also argue that other more modern methods, like computer generated random numbers would be more appropriate.

6.1.1.2 Intention-to-treat vs per protocol analysis

The final analysis in a trial is based on the group of participants with intention-to-treat. For this reason, the value of the randomisation regardless of events followed is preserved. Participants with good compliance who follow the protocol from randomisation to end of the study might be different from those who do not. Consequently, analysis of the per-protocol group only might flaw the results. Furthermore, it is possible that known and unknown factors could have changed since randomisation.

The objective of Paper I-II was to examine participants subjected to infrarenal paraaortic lymphadenectomy, consequently the analyses are based on the per-protocol group. A consort-flow diagram was provided to inform the reader on possible biases of the analyses.

6.1.1.3 Proxy outcomes

The aim of the RASHEC trial was to examine surgical "oncologic safety" of RALS compared to LT in harvesting infrarenal lymph nodes. Number of lymph nodes harvested served as a proxy for proportion detected metastases. We thus assumed that node count and proportion metastases are inherently related. A sample size calculation based on patients with high risk endometrial cancer and paraaortic lymph node metastases resulted in thousands of participants and conducting such a trial was not realistic in a doctoral education. As a result, number of paraaortic lymph nodes harvested was chosen as a proxy, where the power calculation could be precise, the non-inferiority margin based on previous publications and the sample size manageable.

It is important to bear in mind that a proxy outcome does not necessarily translate into a relevant clinical outcome.

6.1.1.4 Internal validity

Internal validity refers to systematic errors or systematic deviations from the truth in a study.

Systematic errors may result in incorrect results and conclusions, i.e. erroneous results because of systematic flaws in study design. Systematic errors remain even if the sample size increases infinitely.

Surgical proficiency is difficult to quantify and the definition of a surgical procedure is often not the same or exact between institutions and surgeons.

Therefore, surgical trials that recruit from multiple sites always carry a problem with internal validity.

Since the RASHEC was a single institution trial with exact definition of the surgical procedures, few participating surgeons and pathologists, one could argue that the internal validity of the study is high. However, only one surgeon performed the RALS procedures versus five for LT why the internal validity can be criticised.

There are three main errors/biases that constitute systematic errors:

6.1.1.4.1 Selection bias

Is defined as when the association between an exposure and an outcome differs between subjects in the study and subjects not in the study. In a RCT, there is a risk of selection bias related to the inclusion and exclusion criteria, a poor randomisation or masking and uneven drop outs/missing data at follow up.

The RASHEC trial was open labelled which may constitute a source of selection bias (see 3.2.1.1. Randomisation). Moreover, to avoid drop outs and protocol violation, the inclusion criteria only permitted healthier and younger participants with ability to understand the written information. Furthermore, of the 143 women assessed for eligibility, eight declined to participate. These are all possible sources of selection bias.

In paper III, the follow up at 12-months post-surgery was unevenly distributed where fewer participants in the laparotomy group completed the HRQoL questionnaires. This might lead to selection bias but also to information bias (see below).

6.1.1.4.2 Information/observation bias

Is defined as errors in measuring an outcome because of poor or flawed collection of data.

Non-differential misclassification is a problem to a lesser extent since the bias is even between groups of comparisons. However, this type of bias can dilute the strength of a real association. There is always a risk of non-differential misclassification in a study.

Differential misclassification is more serious since it is non-proportional and differs between groups of comparisons and can thus create false results. In paper III, the uneven distribution of the

completed HRQoL questionnaires at 12-months post-surgery clearly poses a risk of differential misclassification. The participants in the laparotomy group who did not answer the follow up questionnaires might have been patients with serious symptoms and a decreased HRQoL (or the opposite).

6.1.1.5 Confounders

A confounder is defined as a factor associated with the outcome (but is not a cause of the outcome) and the exposure (but not an effect of the exposure). A confounding factor misleads the interpretation of an association but is not a bias per se, i.e. it does not create untrue associations. In a RCT, the randomisation is the premier way of addressing known and unknown confounders. If confounders are present, they would (ideally) be equally distributed between groups of comparisons. Furthermore, restriction of participants (i.e. to have inclusion/exclusion criteria that minimises distribution of unequal groups) need consideration to avoid confounding. When analysing data, multivariable statistical models can also reduce the risk of confounding.

In Paper II, the proportion of women reporting any extent of self-reported lymphoedema at baseline was uneven despite randomisation. The baseline scores were consequently adjusted for this skewness and thus also the risk of confounding. With a larger sample size in the RASHEC trial, a more even distribution would have been likely. Moreover, on univariable analysis, both surgical modality and abdominal drainage were significantly associated with self-reported LLL at 12 months, but did not remain independently associated in multivariable analysis.

6.1.2 Random error/precision

As opposed to systematic errors, random errors cause imprecise albeit correct results, i.e. large confidence intervals though the true estimate lies within the confidence interval. Larger trials have less risk of random error.

The risk of random error is higher if multiple comparisons are made, since every 20th result depends on chance at a significance level of 5%. There are ways to adjust for multiple testing e.g. Bonferroni correction, where the significance level for multiple testing is corrected and the significance level adjusted.

In paper II, a multivariable analysis was performed and the variables were carefully considered. None of our chosen predictors were significantly associated with the outcome (self-reported lower limb lymphoedema at 12-months post-surgery) why the need to correct for multiple testing was not relevant. Similarly, in paper III, multiple questions were answered within the HRQoL questionnaires without any adjustment for multiple comparisons. Nonetheless, it could be argued that not adjusting for multiple tests is incorrect.

6.1.3 External validity

External validity refers to reproducibility, i.e. would we get the same results in a different population or setting. Participants in a trial may differ from those who do not. They might be younger, healthier, have higher education etc. A multicentre study has a better external validity by definition. Our present study lacks a multicentre design, however, the trial setting was within a population-based health care system with all patients referred to one hospital which strengthens the generalisability, at least in comparison to countries with similar living-standards and health care systems. Nevertheless, external validity is a weakness of the RASHEC trial.

6.1.4 Secondary outcomes from a RCT

Paper II and III solely investigated the secondary outcomes of the RASHEC trial. It is important to emphasise that no power and sample size analysis were conducted for the secondary outcomes. However, a post hoc analysis was performed based on the outcomes of paper II (mean score of self-reported LLL and standard deviation for LT and RALS) resulted in a sample size of 200 women. The actual sample size provided a power of 53%, i.e. the certainty of no mean difference in self-reported lymphoedema score at 12-months between surgical modalities equalled a coin-flip.

6.1.5 Measuring HRQoL

Most data regarding health related quality of life (HRQoL) is binary (yes or no) or ordinal with three or more categories of responses. For comparison between groups, ordinal or binary logistic regression may be applied. The measure of comparison would then be relative (odds ratio) which is difficult to interpret. Furthermore, different scales within a questionnaire would be evaluated with different regression models, which also makes comparisons difficult. For this reason, many questionnaires are transformed to a "continuous" scale (0-100). This transformation enables linear regression where absolute risks (RD and RR) are the measure of comparison. Easier interpretation of the results is thus enabled. Since date in QoL is often very skewed, the assumption of normal distribution for linear regression is almost never met. For this reason, there are non-parametric methods to validate the results from the linear regression [119] .

What does it mean if a comparison of reported HRQoL has a statistically significant difference? Does it correlate to a real-life experienced difference for the patients?

To address this question a minimally or clinically important difference has been introduced. In 1998, Osoba et al validated a "subjective significance questionnaire". Participants rated their perception of change, since answering the EORTC-QLQ-30 questionnaire last.

A 7-category subjective significance questionnaire, ranging from "much worse" to "much better" was evaluated[123]. In addition, the EORTC-QLQ-30 was responded to at the same time.

The mean change in score of the QLQ-30 was then correlated to the 7 categories of answers in the subjective significance questionnaire. The results concluded that a "little" change (for better or worse) in the subjective significance questionnaire correlated to a mean change in QLQ-30 score between 5-9, "moderate" between 10-20 and "very much" greater than 20. The participants of the study were patients with recurrent/metastatic breast cancer or extensive stage small cell lung cancer, recruited from two randomised trials for different chemotherapy regimens. The reproducibility of clinically important difference scores of Osoba et al in early stage gynaecologic cancer patients and in patients not treated with ChT has not been thoroughly investigated. Nevertheless, there is consensus in using these scores.

How do we interpret a clinically important difference not accompanied by statistical significance? If the sample size is small, the chance of this event is high as opposed to the contrary, i.e. risk of a statistically significant difference if the sample size large enough. HRQoL outcomes from a trial must be put in to context and interpreted accordingly.

In the papers from the RASHEC trial we chose to regard mean differences that were *both* statistically significant *and* clinically important as relevant.

6.2 PAPER IV

Paper IV was a non-randomised controlled trial with each woman being her own control. The main outcome was the diagnostic accuracy of a sentinel lymph node algorithm.

6.2.1 Measurements of a diagnostic test - diagnostic accuracy

The accuracy of a diagnostic test primarily depends on three interrelated measures: sensitivity, specificity and prevalence of disease.

The sensitivity measures the proportion of patients with illness that the test has identified (true positive). In the SHREC trial, this translated to number of participants with lymph node metastases that the SNB algorithm detected as compared to gold standard (lymphadenectomy).

The specificity measures the proportion of patients without disease that the test has identified as not having disease (true negative). In the SHREC trial, the specificity was not relevant since false positive SLNs were not possible, see Fig. 19).

Unlike sensitivity and specificity that measures the tests ability to "*spot"* the disease/non-disease, the negative and positive predictive values measure how well a test can *predict* disease/non-disease.

Positive predictive value (PPV) is the probability that subjects with a positive test truly have the disease. In analogy with the specificity, the PPV was not an applicable measure in our trial (no false positives are possible), see Fig. 20.

The negative predictive value is the probability that subjects with a negative test truly do not have the disease. The NPV is dependent on prevalence of disease, and will be higher if the prevalence is low. In the SHREC trial, the NPV is one of two main outcome measures.

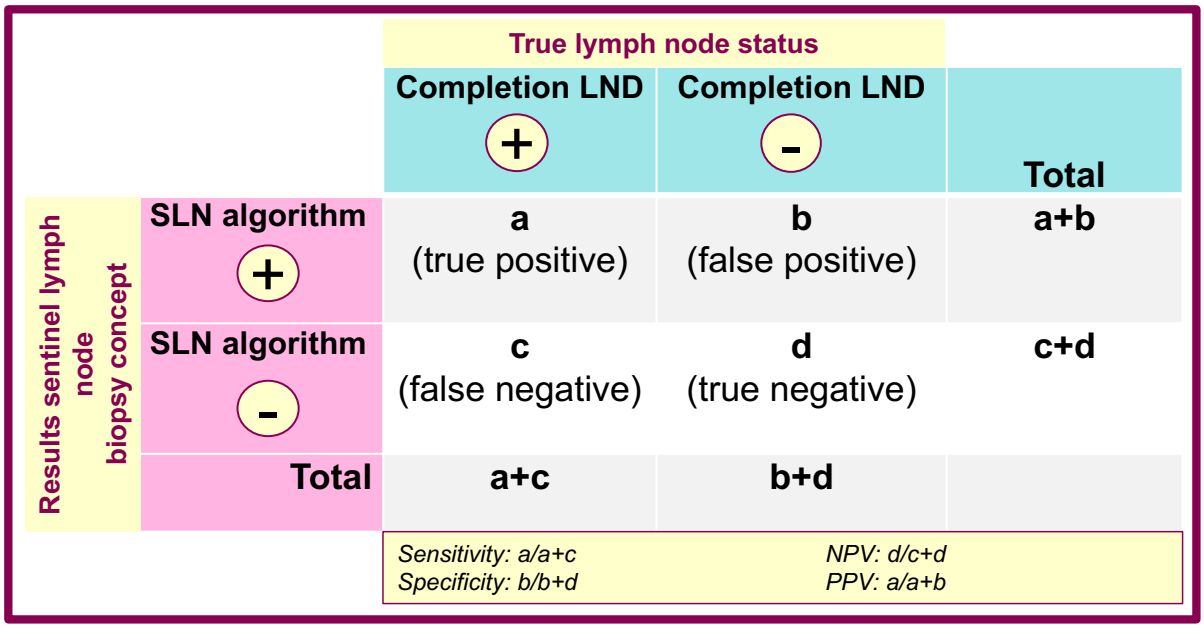

Figure 20. *2x2 table. Abbreviations: SLN; sentinel node; LND, lymphadenectomy.*

There are some aspects of the trial and the NPV that warrants discussion. The NPV was calculated from analysed participants in the per-protocol group, excluding those with isolated paraaortic LNM (*n*=255). One could argue that the 7 participants from the intention-to-treat analysis (excluded after injection of ICG in the uterine cervix) should be included and treated as SNB algorithm negative for metastases. The strength/weakness of the diagnostic test in real life would then truly be investigated. However, of the seven patients excluded after injection of ICG, only two were subjected to lymphadenectomy (without metastases) why the results would not have differed.

6.2.2 Histopathological assessment of sentinel and non-sentinel lymph nodes

3.2.1.1 Differential misclassification

The histopathologic assessment of the sentinel lymph nodes (intervention) were different (ultrastaging) than for the non-sentinel lymph nodes (conventional sectioning). This poses issues

with systematic error per definition. Ideally the non-sentinel lymph nodes should also have been evaluated with ultrastaging. Alternatively, the study could have been designed without ultrastaging of the sentinel lymph nodes to avoid information bias.

3.2.1.2 External validity

The assessment of sentinel lymph nodes with ultrastaging results in increased number of Isolated Tumour Cells (ITC), which are considered to be lymph node metastases in the study.

The clinical implication and prognosis of women with ITC in endometrial cancer is currently unknown. As a result, ultrastaging of sentinel lymph nodes performed in this study results a new entity of lymph node "metastases" with unknown clinical implication, and might therefore flaw the external validity of the trial. For these reasons and to better inform the readers, the paper states that the trial examines the sentinel node biopsy *concept / algorithm* which includes ultrastaging and not only sentinel node biopsy.

There were only five accredited surgeons within two tertiary high volume referral centres that performed the surgeries, why the generalisability of the SHREC study might be compromised.

7 CONCLUSION

- Robot assisted surgery is non-inferior to laparotomy in harvesting infrarenal paraaortic lymph nodes.

- Robot-assisted surgery for extirpation of the inner genitalia with pelvic and infrarenal paraaortic lymphadenectomy is associated with lower health care costs when performed by high-volume surgeons.

- No benefits for robot-assisted surgery over laparotomy was observed for perioperative morbidity and QoL but larger trials are warranted for definitive conclusions.

- Sentinel node biopsy with ultrastaging should replace lymphadenectomy as gold standard for diagnostic lymph node assessment in women with endometrial cancer

8 FUTURE PERSPECTIVES

To date, no trial has answered one of the most important questions for women with endometrial cancer: *does lymph node assessment add any information that can alter their prognosis for the better?*

- There is a need to establish if lymph node assessment is beneficial or not in women with endometrial cancer. A large randomised trial with the intent to give answer to this crucial question started accrual April 2017 and a decade remains until final results (The STATEC trial (https://clinicaltrials.gov/ct2/show/NCT02566811).

- The role of adjuvant treatment in women with stage IIIC EC needs to be investigated.

- The potential therapeutic benefit of extended lymphadenctomy needs to be explored.

9 APPENDICES

9.1 PREVIOUS STAGING ACCORDING TO FIGO

1950-61	1st FIGO staging of endometrial cancer--Clinical
Stage 0	Cases which the pathologist considers most likely to be of a carcinomatous nature though it is impossible to arrive at a definite microscopic diagnosis
Stage I	The growth is confined to the uterus Group 1. Operation advisable Group 2. Bad operative risks
Stage II	The growth has spread outside the uterus

1962-71	2nd FIGO staging for endometrial cancer--Clinical
Stage 0	Histological findings suspicious of malignancy but not proven.
Stage I	The carcinoma is confined to the corpus.
Stage II	The carcinoma has involved the corpus and cervix.
Stage III	The carcinoma has extended outside the uterus but not outside the true pelvis.
Stage IV	The carcinoma has extended outside the true pelvis or has obviously involved the mucosa of the bladder or rectum

1971-88	3rd FIGO staging for endometrial cancer--Clinical
Stage 0	Carcinoma in-situ. Histological findings suspicious of malignancy.
Stage I Ia Ib	The carcinoma is confined to the corpus. The length of the uterine cavity is 8 cm. or less. The length of the uterine cavity is greater than 8 cm.
Stage II	The carcinoma has involved the corpus and cervix.
Stage III	The carcinoma has extended outside the uterus but not outside the true pelvis.
Stage IV	The carcinoma has extended outside the true pelvis or has obviously involved the mucosa of the bladder or rectum
	It is desirable that Stage I cases be sub grouped with regard to the histological type of the adenocarcinoma as follows: G1. Highly differentiated adenomatous carcinoma G2. Differentiated adenomatous carcinoma with partly solid area. G3. Predominantly solid or entirely undifferentiated carcinoma

1988–2009	4th FIGO staging for endometrial cancer-- Surgical
Stage I IA IB IC	Tumour limited to the uterus. Tumour limited to the endometrium. Invasion <50% of the myometrium Invasion ≥50% of the myometrium
Stage II IIA IIB	Extension to the cervix but not beyond the uterus. Endocervical glandular involvement only. Cervical stromal invasion.
Stage III IIIA IIIB IIIC	Extension outside of the uterus/cervix with/without regional metastasis. Tumour invades serosa or adnexa or positive peritoneal cytology. Vaginal metastasis. Metastasis to pelvic and/or paraaortic lymph nodes
Stage IV	The carcinoma has extended outside the true pelvis or has obviously involved the mucosa of the bladder or rectum

9.2 SUMMARY OF INFLUENTIAL CLINICAL STUDIES AND TRIALS IN EC

Name/year/Author/ Country	Number[1]	Study Design	Intervention	Comparator	Stage	Lymphadenectomy Required	Definition of high risk if stage I-II/Included	% IIIC	Primary Outcome Results[2]	Comment
GOG33 1987 Creasman et al USA	621	Descriptive	N.A	N.A	I FIGO 71	Yes, pelvic and PA= "fat pad over the major vessels proximity to the renal vessels"	Low risk: (<5%) Intramucosal all grades, grade 1 with invasion (not type 2) Moderate risk: (5-10%) grade 2 with invasion, grade 3 <50%MI High risk: (>10%) grade 3 >66% MI + Type 2 For PA LNM only grade 3>66% at high risk all other low risk	N.A	N.A	22% of clinical stage I have disease outside uterus. Intramucosal: 0% risk Suggests frozen section for MI assessment perop. 2% isolated PALNM In total 9% PLNM, 6% PALNM, 5% Adnexal met, 6% intraabdominal disease
PORTEC-1 2000 Creutzberg Netherlands	714	RCT	No adjuvant	EBRT Pelvic	I FIGO 88	No LND	Included; Grade 1>50% MI Grade 2 Grade 3 <50% MI	N.A	LRR: 86 vs 96% (s) OS: 81 vs 85% (ns)	Less LRR in EBRT group (4 vs 14%) but the same proportion of distant metastases (7-8%)
GOG-99 2004 Keys et al	392	RCT	No adjuvant	EBRT Pelvic	IA-C, IIA-B FIGO 88	Yes GOG manual	First" Intermediate risk"; Endometrioid with MI and without LNM.	N.A	RFS: 88 vs 97% (s)	Less LRR in EBRT group (2 vs 9%) but the same proportion of

USA			treatment				The expected relapse rate of 25% not met why a new category was found; High Intermediate Risk; 1. Grade 2-3 + LVSI+>66% MI 2. > 50 years with 2 of above 3. >70 years with 1 of above		OS: 86 vs 92% (ns)	distant metastases (6 vs 5%). HIR group w/o EBRT 27% recurrence risk at 48 months follow up despite LND and negative lymph nodes.
GOG-122 2006 Randall et al **USA**	396	RCT	CT	EBRT Whole Abdomen	III/IV intraabdominal only FIGO 88	Yes GOG manual	N.A	49% of stage III/IV	PFS: 50 vs 38% (s)	Residual intraabdominal disease <2 cm included HR PFS 0.71 (95% CI, 0.55 -0.91) in favour of CT. HR OS 0.68 (95% CI, 0.52- 0.89) in favour of CT. OS: 55 vs 42% 65% of stage III were stage IIIC PFS/OS not significant for stage IIIC
2006 Maggi et al. **Italy**	345	RCT	CT	EBRT Pelvic	I, II, III FIGO 88	Yes "With or without selective pelvic and lumbo-aortic sampling"	Definition high risk IC endometrioid grade 3 II endometrioid grade 3 with MI>50% III endometrioid	22% of all 34 % of st III	OS: 66 vs 69% (ns) PFS both groups 63% (ns)	No subgroup analysis for stage IIIC
JGOG 2008	385	RCT	EBRT	CT	IC-IIIC FIGO 88	Yes	Endometrioid >50% MI (regardless of stage)	12% of all	OS: 85 vs 87% (ns)	PALND performed in 29% (4% PALNM)

Susumu et al **Japan**			pelvic			"Surgical staging consisted ideally of pelvic and/or paraaortic lymphadenectomy".				PLND performed in 96% (12% PLNM) Subgroup analysis for **HIR**, defined as 1. stage IC patients over age 70 years or having G3 endometrioid adenocarcinoma or 2. stage II or IIIA with deeper than 50% MI. Significant better OS for CT group 90% vs 74%
Benedetti-Panici et al 2008 **Italy**	514	RCT	PLND	No PLND	I FIGO 88		Included: Endometrioid histology with MI. Excluded: Grade 1 with less than 50% MI upon intraoperative frozen section.	13% in PLND group	OS 86 vs 90%(ns)	No. harvested LN median 30. Frozen section analysis, only 8 patients did not have MI at final pathology. Only 7% grade 1 Well balanced adjuvant treatment DFS: 81 vs 82% (ns)
Mariani et al 2008 **USA**	422	Descriptive	N.A	N.A	N.R	PLND+ IRPALND	Low risk: G 1+2, <50% MI, < 2 cm size All other high risk	22% of high risk	N.A	72% of patients subjected to LND. Of the 22% who had LNM; 51% both PL and PA 16% isolated PA 33% only PL

										77% of pan with PA met had disease above IMA. Median PLN 35 Median PALN 17
SEPAL 2009 Todo et al **Japan**	671	Retrospective Cohort study	PLND+PALND	PLND	All stages FIGO 88	Systematic PLND or PLND+ IRPALND	Low risk: Stage IA-B, Grade 1-2, neg. LVSI Intermediate risk: Stage IA grade 3 Stage IB grade 1-2 with LVSI Stage IB grad 3 Stage IC Stage II High risk: Stagey III and IV Carcinosarcoma not included	20% of PLND 25%of PLND+ IRPALND	OS in high and intermediate risk: 83 vs 73% (s) OS low risk: 96 vs 94 (ns)	No. harvested lymph nodes: PLND arm: median 34 PLND +IRPALND: pelvic median 59 and PA median 23 Adjuvant treatment PLND vs PLND + IRPALND: EBRT: 23% vs1% CT: 27% vs 47%
MRC-ASTEC 2009 Kitchener et al **UK South Africa Poland New Zeeland**	1408	RCT	PLND	NO PLND	I, II FIGO 88	Obturator and iliac nodes	Low-risk: FIGO IA or IB, G1+2 Intermediate-risk and high-risk: Stage IA - IB with grade 3 Serous or clear cell *(Carcinosarkoma excluded)* Stage IC or IIA High risk advanced: ie, spread beyond the uterine corpus (stage IIB, IIIA, IIIB, and IV). Stage IIIC not included.	N.R.	OS: 80 vs 81% (ns)	No. harvested LN median 12. 35% <10 LN.
Pooled analysis MRC-ASTEC+ NCIC CTG EN.5	905 (709 from AST EC	RCT	EBRT pelvic	No EBRT	I, II FIGO 88	Obturator and iliac nodes if randomis	Intermediate or high risk only including: Stage IA-IB grade 3 IC Non-endometrioid histology	N.R.	OS: 84% in both groups	>95% Intermediate and high risk 32-38% had LN assessment of these

2009 Blake et al **UK Poland New Zeeland Canada Norway USA Australia**	and 116 from EN.5)					ed to LND in ASTEC Optional in EN.5	*Carcinosarcoma excluded* PALN metastases exclusion criteria Pelvic lymph nodes could be negative or not examined; women with positive pelvic lymph nodes were eligible for ASTEC but not for EN.5			4% had nodal involvement = low Median node count 10 LN, well-balanced between the groups.
Pooled analysis NSGO/EORTC and the MaNGO-Iliade **Högberg et al.** **2010** **Europe**	534	RCT	EBRT pelvis+CT	EBRT pelvis	See High risk definition FIGO 88	"LND optional"	NSGO: Stage I with "profile" that qualified for adjuvant treatment + amendment 2002 also stage II + IIIA + IIIC (only pelvic not PA) (PALNM = exclusioncriteria) MaNGO: Endometrioid only stage IIB, IIIA–C disease (stage IIIA with positive cytology alone without other risk factors were not included)	12% av all (1%in NSGO) 61% of stage III	OS: 82 vs 75% (ns) PFS: 78 vs 69% (s)	26% had PLND OS: close to significant (CI: 0.46-1.03) PFS: In subgroup analysis only (s) if endometrioid histology and no LND. CSS: 87 vs 78% (s)
PORTEC-2[11] 2010 Nout et al **Netherlands**	427	RCT	VBT	EBRT pelvic	I-IIA FIGO 88	No	High intermediate risk: 1. age> 60 years and stage 1C grade 1 or 2 2. stage 1B grade 3 3. stage 2A, any age	N.A	Vaginal recurrence: 1.8 vs 1.6% (ns)	LRR: 2.1 vs 5.1% (ns) Distant recurrence: 8 vs 6 % (ns) OS: 85 vs 80% (ns)

GOG-258 Only Abstract ASCO 2017 Matei et al. **USA Clinical trials: NCT00942357.**	733	RCT	CC-CT+ EBRT followed by CT	CT only	III IVA I-II FIGO 2009	PLN sampling and PALN sampling optional	For stage I-II: Non endometrioid (except carcinosarcoma) with positive cytology washings	N.R	RFS: Only HR 0.90 (ns) reported	<2 cm residual was allowed. CC-CT+EBRT less recurrence: Vaginal 3 vs 7%(s) Pelvic and paraaortic 10 vs 21% (s) Distant recurrence better for CT only 28 vs 21% (ns) OS not reported yet premature
GOG-249 Only Abstract ASTRO 2017 Randall et al **USA** **Clinical trials: NCT00807768.**	601	RCT	CT + VBT	EBRT pelvic	I, II FIGO 2009	Pelvic and paraaortic lymphadenectomy are optional	For stage I-II (high intermediate risk): Stage I (+ endocerv glandular) • Endometrioid grad 2 or 3 • LVSI + • >50% MI Age>= 70 with 1 risk factor Age>=50 with 2 risk factors Age>=18 with 3 risk factors Non endometrioid histology (carcinosarkoma excluded) Stage II Any histology	N.R	RFS: 82% for both groups (at 3 years)	3-year OS 88 vs 91% (ns) 5-year LRR in pelvic and paraaortic nodes 9 vs 4% (s) 5-year distant (18%) and vaginal recurrence (2%) no difference (18% both groups for distant)

PORTEC-3[12] 2018 De Boer et al **Multination al 103 participatin g centers**	660	RCT	CC-CT+ EBRT follo wed by CT	EBRT pelvic	I-III FIGO 2009	LND, whether systemic or sampling, was left to the discretion of participati ng centers. Not defined	High Risk: stage IB, grade 3 or LVSI (or both) stage II-III endometrioid stage I-III no serous or clear cell histology	N.R	OS: 82 vs77% (ns) FFS: 76 vs 69% (s)	15% had some form of LND. OS stage III 79% vs 70% (ns) FFS stage III 69 vs 58% (s) Data on number of LND proportion stage IIIC unfortunately not reported

Abbreviations: N.A, Not Applicable; FIGO, International Federation of Gynecology and Obstetrics; MI, Myometrial Invasion; PA, Para Aortic: LNM, Lymph Node Metastasis; perop., during surgery; PALNM, Para Aortic Lymph Node Metastasis; PLNM, Pelvic Lymph Node Metastasis; RCT, Randomised Controlled Trial; EBRT, External Beam Radiation Therapy; LND, Lymph Node Dissection; LRR, Loco Regional Recurrence; (s), significant; OS, Overall Survival; (ns), not significant; RFS, Recurrence Free Survival; HR, Hazard Ratio, HIR; High Intermediate Risk, w/o, without; CT, Chemo Therapy; PFS, Progression Free Survival; DFS, Disease Free Survival; PL, Pelvic; N.R, Not Reported; IRPALND, Infra Renal Paraaortic Lymphadenectomy; neg., negative; LVSI, Lymph Vascular Space Invasion; No., number; CSS, Cancer Specific Survival; VBT, Vaginal Brachy Therapy; CC, concomitant; FFS, Failure Free Survival.

[1]Number of patients evaluated

[2]Intervention reported first (intervention vs comparator)

10 ACKNOWLEDGEMENTS

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